File No: NA/901

June 2001

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Dialkylene Glycol Ether

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Director
Chemicals Notification and Assessment

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FULL PUBLIC REPORT

DIALKYLENE GLYCOL ETHER

1. APPLICANTS

Dow Chemical (Australia) Ltd (A.C.N 000 264 979) of 541-583 Kororoit Creek Road ALTONA VIC 3018; Ezifloor Products (A.C.N 085 852 198) of 36 Sydenham Road, NORWOOD SA 5067; Peter Wait Pty Ltd (A.C.N 010 645 780) of 2/39 Devlan Street MANSFIELD QLD 4122; and BonaKemi Australia Pty Ltd (A.C.N 096 221 448) Level 48, 101 Collins Street MELBOURNE VIC 3000 have submitted a standard notification statement in support of their application for an assessment certificate for dialkylene glycol ether.

2. IDENTITY OF THE CHEMICAL

The chemical name, CAS number, molecular and structural formulae, molecular weight, spectral data, details of exact import volume have been exempted from publication in the Full Public Report and the Summary Report.

Marketing Name: Dialkylene glycol ether.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C & 101.3 kPa:	Colourless liquid, mild odour: - ethereal
Boiling Point:	175°C
Freezing Point:	< -71°C
Specific Gravity:	0.904 g/cm^3 at 20°C
Vapour Pressure:	0.72 kPa at 20°C 1.08 kPa at 25°C
Water Solubility:	526 g/L at 20°C
Partition Co-efficient (n-octanol/water):	log P_{ow} 0.42 at 20°C

Hydrolysis as a Function of pH:	Hydrolytically stable
Adsorption/Desorption:	Minimal – see comments below
Dissociation Constant:	Not determined – see comments below
Flash Point:	65ºC
Flammability Limits:	Upper Explosive Limit = not determined; Lower Flammability Limit (vol% in air): 0.85 (calculated).
Autoignition Temperature:	165°C
Explosive Properties:	Not explosive
Reactivity/Stability:	Non-reactive. Will form peroxides if antioxidant not added.
Fat Solubility:	Completely miscible
Surface Tension:	64.3 mN/m for a 1.12 g/L aqueous solution at 20°C
Trophospheric half life:	3.818 hours (calculated)
Particle size:	Substance is a liquid.

3.1 Comments on Physico-Chemical Properties

The boiling point was determined using a melting point apparatus (OECD TG 103) at 101.5 kPa (RCC-NOTOX 1989g).

The analysis for the freezing point was performed using a jacketed sample tube containing the notified chemical and cooling it with dry ice in acetone (OECD TG 102) (RCC-NOTOX 1989j). The substance remained a colourless liquid and no sign of freezing was observed down to the minimum of –71ºC.

The density was determined using the pycnometer method (OECD TG 109) (RCC-NOTOX 1989h).

Vapour pressure was performed in a twin ebulliometer, using diphenyl oxide as the reference substance (The Dow Chemical Company 1989).

Water solubility was determined using the flask shaking method (OECD TG 105) with gas chromatography analysis on the two isomers of the substance (RCC-NOTOX 1989n). Isomer 1 had a solubility of 289 g/L and Isomer 2 had a solubility of 237 g/L. The water solubility of the notified chemical was the sum of the solubilities of the two isomers.

Hydrolysis potential of the notified chemical was tested in accordance with EEC method C.10 at pH 4, 7 and 9 (RCC-NOTOX 1989k). After 5 days no decrease in concentration occurred in any of the test solutions so it was concluded that the substance is hydrolytically stable. It is accepted that hydrolysis is unlikely as the chemical contains no hydrolysable functional groups. Ethers are known to be resistant to hydrolysis under environmental conditions (Howard 1993).

The partition coefficient was determined using standard methodology (OECD TG 107) with gas chromatogram analysis (RCC-NOTOX 1989l).

The adsorption of the notified chemical to soil was determined using the preliminary test of OECD TG 106 (Environmental Chemistry Research Laboratory 1998). Solutions containing the notified chemical were mixed with three different soils of differing properties (pH, cation exchange capacity, clay content and organic matter – see table below) for 16 hours at 22^{o}C and analysed using gas chromatography with flame ionisation detection. It was found that <5% adsorption occurred in all test solutions so it was determined that the substance has 'minimal' adsorption to soils.

Soil	***% Adsorbed***	***pH***	***% OC***
Sand (I)	0-3.4	5.4	0.98
Silt Loam (II)	1.2-4.3	6.1	1.33
Silt Loam (III)	0	7.6	0.7

The fat solubility of the substance was determined at various ratios ranging from 100 to 0.01 [OECD TG 116] (RCC-NOTOX 1989i). The substance was found to be totally miscible with fat at 37^{o}C at all ratios tested.

Surface tension was determined using a Kruss tensiometer [OECD TG 115] (RCC-NOTOX 1989m). The substance is not regarded as surface active.

The notified chemical is classified as a combustible liquid according to AS 1940 (Standards Australia 1993).

4. PURITY OF THE CHEMICAL

Degree of Purity: Very high. Details claimed as exempt.

Hazardous Impurities: None.

Non-hazardous Impurities (> 1% by weight): None.

Additives/Adjuvants: Less than 1%. Details claimed as exempt.

5. USE, VOLUME AND FORMULATION

The notified chemical will not be manufactured in Australia. The notified chemical will be imported from USA or Europe at up to 100 tonnes in year 5. It is expected that approximately 90% of the imported notified chemical will be in formulated products and 10% will be imported as commercial grade quality (very high purity) for reformulation in Australia.

The uses of the notified chemical are tabulated below.

Application	*Use Description & % Concentration in Final Product*
Professional Cleaning Wipes:	Wipes used for cleaning up laboratories. (% concentration not provided)
Two-part water & solvent based polyurethane coatings:	Used as a formulation ingredient to dissolve the isocyanate (in part A of the two-part system); (20%).
One component polyurethane dispersions:	Used as a formulation additive in dispersion polymerisation reaction; (5%).
Synthesis of alkyd and polyester resins:	Used as the medium for this reaction; (50%).
Industrial cleaning formulations e.g. cleaners for electronic circuit boards:	Used as a minor ingredient in water and solvent based cleaning formulations; (10%).
Chemiluminescence solvent media:	Media for chemiluminescence products; (70%).
Paint stripper formulations:	Active solvent in paint stripper formulations; (30%).

The principal notifier will import commercial grade quality notified chemical. The co applicants will import formulated water based 2-part polyurethane coatings where the notified chemical is an ingredient in the hardener.

Commercial grade notified chemical is imported by sea packaged in 200 litre mild steel drums. After unloading from ship the drums are transported by road to a distributor's warehouse where they are unloaded and stored in a warehouse until required by the end user. The required quantity of drums of the notified chemical shall be transferred by road transport to the end user on request, unloaded and stored on their site until required for use.

As the notified chemical has yet to be marketed in Australia no firm market research data is available to confirm that formulated product applications will align with the forecast usage. Importation details for formulated products are not available.

6. OCCUPATIONAL EXPOSURE

The notified chemical may be imported as commercial grade quality or as an ingredient of a formulated product. The table below identifies potential exposure to the notified chemical in each of the identified end uses of the notified chemical.

Application	*Potential for exposure during final product use*
Professional cleaning wipes	Dermal exposure during cleaning operation.
Two-part water & solvent based polyurethane coatings	During application skin and vapour exposure. After application of film exposure mainly to vapours.
One component polyurethane dispersions	Minimal quantities compared to two-part system. Exposure during evaporation expected to be small.
Synthesis of alkyd and polyester resins	Exposure during formulation of resin into paint. Also, final paint drying during evaporation
Industrial cleaning formulations e.g. cleaners for electronic circuit boards	Exposure to vapours during evaporation of cleaner. Relative exposure should be low.
Chemiluminescence solvent media	System is closed. Exposure should be nil. (i.e. glow sticks)
Paint stripper formulations	Skin exposure to liquid and inhalation exposure to vapours during stripper application.

6.1 COMMERCIAL GRADE QUALITY

Transportation and Storage
One to two drivers per year could be involved in the transport of the 200 litre drums from wharf to the distributor's site based on the upper limit of imported quantity. At the distributor's warehouse any one of six employees per annum could be involved.

When drums of the notified chemical are transferred by road to the end user's site, one of six forklift operators could be involved in the loading of a drum or drums onto trucks and one of several different drivers per year used for delivering the product to the customer.

At the customer's warehouse drums of the notified chemical will be unloaded and stored until required for use in the formulating plant. It is anticipated that this task would be spread over two forklift operators per customer throughout the year.

In all the above material handling processes workers are not exposed to the notified chemical during normal drum handling operations, as the drums remain sealed. For abnormal situations, such as a

spill or fire resulting from an incident, the personnel involved are trained in the emergency procedure relevant to the type of incident.

The employees at the distributor's warehouse are trained in the safe handling of chemicals and emergency procedures for both spills and fire. The Material Safety Data Sheet (MSDS) for the notified chemical will be reviewed with relevant employees before the notified chemical is stored in the warehouse. The MSDS shall be readily available to employees.

Formulating Site

Formulation of Cleaners and Paint Strippers

This section assumes that the 10% of the imported notified chemical, eventually imported as commercial grade product, will be formulated into industrial cleaners and/or paint stripper products. The formulation process is usually a batch process in a closed vessel operating at atmospheric pressure. The notified chemical is added using a powered drum pump, a hand operated hand pump or decanted into a container and added manually at the appropriate stage of the formulation procedure and mixed by mechanical agitation. There is a potential during these types of operation for skin contact when handling the drum pump or decanting into a container. In addition there is the possibility of eye contact if the notified chemical drips from the drum pump during handling. After the addition of other ingredients, and further mixing a sample of the formulated product is taken for testing. The final product is transferred to storage tanks for later packaging into containers of varying capacity for industrial and commercial markets. Cleaning and maintenance of equipment would occur thereafter.

Assuming a batch size of 2000 L, the notifier estimates time of potential exposure as:

Transfer of liquid from drums to storage:	20 minutes per drum when handling the air pump.
Sampling by process operator:	5 minutes per batch

Number of personnel involved per batch:

Transfer of liquid from drums to feed storage tank	1
Sampling:	1

Number of batches per year:

1st year:	0
After 1st year:	20

Estimated total potential exposure times,

During transfer operations (years 2 to 5): = 1 operator x 0.3 (hour) x 20 = approximately 6 hours per year at peak production.

Sampling (years 2 to 5) = 1 operator x 1/12 (hour) x 20 = 1.6 hours per year at peak production.

Thus potential exposure would be approximately 8 hours per year in years 2 to 5 for an operator i.e. less than 1% of annual work hours.

Most likely exposure during production of a formulated product is skin contact.

Potential exposure when packaging product

During packaging operation one or two operators could be involved for two hours per batch i.e. 160 hours in years 2 to 5. Overexposure is not expected during normal semi or fully automatic packaging operations ~~at~~ as the concentration of the notified chemical in the final product is between 10 and 30% and significant exposures by skin, eye contact, or inhalation is not expected during this process. If a spill occurs during packaging, exposure is not significant as the atmospheric concentration of the notified chemical at saturation in a confined space is calculated to be about 700 ppm at 20°C.

Estimating that a spill occurs ~~over~~ only 1% of the packaging time and one operator is involved, the estimated potential exposure period to a spill is approximately 1.6 hours per year spread over 20 packaging runs per year or an average of 5 minutes per packaging run.

The most likely exposure route resulting from a spill of formulated product during packaging is skin contact.

Summary

Transportation - At peak quantities:

Activity	*Number of Workers*	*Potential Exposure*	*Exposure Period*
Transportation wharf to store	1 of several	Nil	None
Handling at store	1 of 6	Nil	None
Transport to customer	1 of several	nil	None

Note. The number of personnel assumes one individual or several different individuals involved on any one day for each activity.

Formulating - At peak formulation volume 20 batches per year.

Activity	*No. of workers*	*Potential Exposure Period per batch*	*Total potential exposure period per year*	*Personal protective equipment*
Product reception & storage	1 – 2	Nil; sealed drums	None expected	
Operator – liquid transfer	1	20 minutes per drum per batch	8 hours at peak production/exposure	
Operator - sampling	1	5 minutes per batch	1.6 hours at peak production/exposure	Overalls, protective (butyl rubber) gloves ; eye protection.
Operator – filling & packaging	1 - 2	2 hours per batch	160 hours at peak packaging/exposure	
Operator – Cleaning up spill during packaging	1 - 2	Average 5 minutes	1 – 2 hours per annum	

6.2 IMPORTED FORMULATED PRODUCTS

At the time of assessment, estimates of the number of workers directly involved in the application of the formulated products are unknown.

7. PUBLIC EXPOSURE

The undiluted notified chemical is not available for direct sale to the public. The potential for public exposure to the notified chemical during transport, reformulation or disposal is assessed as low. The majority of the notified chemical will be used in industrial applications. However, both paint strippers and chemiluminescent products that contain the notified chemical will be available to the public. Some members of the public may make dermal and inhalation contact with paint strippers containing the notified chemical, however, exposure is likely to be brief and intermittent. Exposure to the notified chemical in chemiluminescent products is unlikely under normal circumstances since (according to the example provided by the notifier) the notified chemical is contained within a closed system

8. ENVIRONMENTAL EXPOSURE

8.1 Release

The principal notifier claims that most of the notified chemical will be disposed of through use, primarily by evaporation to the atmosphere (79%) and discharge to the water compartment (13%) and landfill (8%). Environmental exposure from drum residues of the chemical is expected to be small (possibly up to 0.1% or 100 kg per annum) relative to volumes used. Empty drums will be reconditioned and recycled by drum reconditioning companies, or alternatively salvaged as scrap metal. It is claimed that the import drums have high reconditioning value.

Cleaning Products

The notifier estimates that 20 batches per annum of the paint stripper formulation will be produced at one site only (site is not named). Each batch could be up to 2000 L. During formulation and clean-up, waste chemical may be discharged to an on-site trade waste water treatment plant or to the sewer. Losses would be minimised by the highly automated formulation and packaging processes. The notifier estimates that one kg per run wash will be lost or up to 10 kg per annum (2 batches per day) during equipment cleaning. No information was provided regarding spills and clean-up, but it can be assumed that spills would usually be contained by the plant bunding and most of the notified chemical would evaporate during the cleaning process.

Rinse water containing the notified chemical will be discharged to the sewer during use as commercial surface cleaning products and paint strippers. The notifiers have anticipated that 75% of the industrial cleaners and 50% of the paint strippers will be released to water during use. This equates to up to 10 tonnes per annum of the notified chemical from industrial cleaners and up to four tonnes from the paint strippers. Product packaging will likely be disposed of to landfill. The notifiers did not supply details of expected residues remaining in the containers, but environmental exposure from this is expected to be low compared with the volume used.

From its use in professional wipes for laboratory cleaning the notifier estimates that up to one tonne per annum of the notified chemical will be disposed of to landfill.

Coatings
No reformulation of the coating products will occur in Australia as they are imported as final products, ready for use in the marketplace as polyurethane coatings and resins and chemiluminscent products. The notifiers did not detail the application methods expected, but it is assumed that application will be mainly by spray, roller or brush. During such use the notifiers expect that the notified chemical will be slowly released directly to the atmosphere as the applied film sets and hardens. A small quantity of waste would be expected (up to 0.2% or less than 160 kg per annum) to be generated from equipment and work area clean-up, which is expected to be discharged to the sewer or buried in a trade waste or general waste landfill.

It is expected that empty coatings packaging will be disposed of to either trade waste or municipal waste landfills by the consumers after use. The notified chemical will either evaporate to the atmosphere as the coating dries, or otherwise remain with the product inside the container.

Other Applications
Additionally, the total volume of chemical used in chemiluminescent applications (up to 10 tonnes per annum) is expected by the notifier to be released to land, presumably as waste to landfill.

8.2 Fate

When the notified chemical is used as a component of a cleaning or paint stripping product most of the chemical is likely to be discharged to sewer where it will be treated at the sewerage treatment plant before discharge via outfall to the aquatic environment. Here it is likely to remain in the aquatic compartment, with only a very minor amount likely to be adsorbed to sludge or evaporated to air. This prediction is derived using the Simple Treat method which compares log P_{ow} (0.42) to log H (-1.6) and indicates that 100% chemical should remain in water with little to no evaporation or adsorption to sludge.

Most notified chemical is used as a component of a floor coating or resin is expected to be released directly to the atmosphere via evaporation as the product dries. The notifiers expect the evaporated notified chemical to be broken down in the troposphere, with a predicted half-life of 3.8 hours using the SRC – AOP for Microsoft Windows, v1.90 atmospheric half-life estimating software. It is estimated that 1% of the average amount released daily to the atmosphere remaining in the air after one day. The notified chemical does not contain the halogens required for ozone depletion in the stratosphere and is not expected to contribute to smog formation, ozone depletion or global warming. The notified chemical is water soluble and has a low vapour pressure. It is not expected to persist in the atmosphere long enough to undergo significant photochemical reaction and smog formation.

Products of incineration will include water and oxides of carbon.

The chemical was determined to be ultimately biodegradable, with 250 and 252 mg/L solutions being degraded by 25% within 28 days, in the Modified Zahn-Wellens Test for Inherent Biodegradability (OECD TG 302B) (RCC-Umweltchemie AG 1992). The reference material, aniline, was degraded by 92% after 7 days.

The chemical was tested for its ready biodegradability with pre-adapted inoculum in the Modified Sturm Test (OECD TG 301B) (RCC-NOTOX 1989f). Biodegradation was not sufficient for the notified chemical to be classified as readily biodegradable with pre-adaptation of inoculum, with

18% and 32% degradation observed at 10 and 20 mg/L, respectively. Under the same test conditions the reference material, sodium acetate, was degraded 70% within 16 days.

Considering these results, it is expected that the notified chemical would not be highly persistent and should undergo substantial biodegradation in the environment. The notified chemical's high water solubility will also limit its bioavailability and hence bioaccumulation (Connell DW 1989).

The notified chemical was tested for bioconcentration in rainbow trout in two separate studies (Environmental Toxicology & Chemistry Research Laboratory 1992). The trout were exposed to the test substance (^{14}C-uniformly labelled) at 6.5 and 0.67 µg/L under flow-through conditions for 14 days. After the uptake phase, the fish were transferred to clean flowing water for 28 days. Periodic samples were taken and analysed for ^{14}C radioactivity. The calculated bioconcentration factor was 4 mL/g in both the studies. This result indicates that the chemical has little potential for bioconcentration in aquatic organisms. The estimated time required to achieve 90% of exposure steady-state was 35-58 days. When the fish were moved to clean flowing water the ^{14}C had an elimination half-life of 11 to 17 days.

The notified chemical was also tested for its uptake and elimination in rainbow trout (Environmental Toxicology & Chemistry Research Laboratory 1998). The trout were exposed to the test substance (^{14}C-uniformly labelled) at an average exposure of 1.83 µg/L under flow-through conditions for 43 days. After the uptake phase the fish were transferred to clean flowing water for 98 days. Periodic samples were taken and analysed for ^{14}C radioactivity. The calculated bioconcentration factor was 4.3, 3.7 and 4.0 mL/g for whole fish, muscle and remainder, respectively. When the fish were moved to clean flowing water the ^{14}C residues showed $t_{1/2}$ (α phase) of 2.7, 0.36 and 0.96 days for whole fish, muscle and remains, respectively. The β phase was much longer, being ~77 days for all three tissue types. This result indicates that the chemical has little potential of bioconcentration in aquatic organisms. However, the lengthy elimination time involved in both tests indicated a very slow clearing from tissue and in the second test the slow observed decrease in the β phase may only have occurred by growth dilution rather than elimination from tissues.

9. EVALUATION OF TOXICOLOGICAL DATA

In some toxicity studies the CAS number identified in the study report represents one isomer of the notified chemical. The notifier is uncertain as to why this has been recorded as so but substantiates that the test substance used is the notified chemical, that is, a mixture of isomers.

Summary of the toxicity of dialkylene glycol ether

Test	*Species*	*Outcome*
Acute Effects		
Acute oral toxicity	Rat	$LD_{50} \geq 3330$ mg/kg bw
Acute dermal toxicity	Rat	$LD_{50} > 2000$ mg/kg bw
Acute inhalation	Rat	$LC_{50} > 5.3$ mg/L/4 hour
Skin irritation	Rabbit	Slightly irritating
Eye irritation	Rabbit	Slightly to moderately irritating
Skin sensitisation:	Guineapig	
adjuvant method		Non sensitising;
non-adjuvant method		Mildly sensitising.
Repeat Dose		
Oral, gavage 28 day	Rat	NOAEL 100 mg/kg/day
Oral, drinking water 14 day palatability study	Rat	NOAEL 500 mg/kg/day
Oral, drinking water 28 day	Rat	NOAEL 500 mg/kg/day
Inhalation, 2 week	Rat	NOAEL 70 ppm
Inhalation, 13 week	Rat	NOAEL 50 ppm
Developmental		
Probe study, oral, gavage	Rat	NOAEL, maternal toxicity 100 mg/kg/day; NOAEL, developmental effects,500 mg/kg/day.
Oral, gavage	Rabbit	NOAEL, maternal toxicity, 100 mg/kg/day. NOAEL, developmental effects, 250 mg/kg/day
Inhalation	Rat	NOAEL, maternal toxicity & developmental effects, 225 ppm.
Reproduction		
Oral, drinking water, 2-generation	Rat	Parental NOAEL, systemic effects, 50 mg/kg/day; NOAEL, reproductive effects, 1000 mg/kg/day; NOAEL, neonatal toxicity 250 mg/kg/day.
Genotoxicity		
Reverse mutation	*S. typhimurium*	Non-mutagenic
Forward mutation	CHO cells	Non-mutagenic
Chromosomal aberration, *in vitro*	Lymphocytes	Non-clastogenic
Induction of micronuclei, *in vivo*	Mouse	Non-clastogenic

9.1 Acute Toxicity

9.1.1 Oral Toxicity (RCC-NOTOX 1989e)

Species/strain:	Rat/Wistar
Number/sex of animals:	5/sex/dose
Observation period:	14 days
Method of administration:	2000, 2800, 3750, or 5000 mg/kg by oral gavage, administered in dose volumes of 2.21, 3.09, 4.14, 5.13 mL/kg, respectively.
Test method:	OECD TG 401; EC Method B1
Mortality:	2 000 mg/kg: 1 male; 2 800 mg/kg: 1 male, 2 females; 3 750 mg/kg: 2 males, 5 females; 5 000 mg/kg: 4 males, 4 females.
Clinical observations:	2000 mg/kg : lethargy. 2800 mg/kg : lethargy, absence of reaction, comatose, convulsions, rales and piloerection. 3750 mg/kg : lethargy, absence of reaction, comatose. 5000 mg/kg: lethargy, absence of reaction, bradypnoea, dacryorrhoea. Bodyweight loss was noted at death for animals at 2000 mg/kg or 5000 mg/kg and during the first week of observation for surviving males receiving 3750 mg/kg. All surviving animals showed bodyweight gain over the observation period.
Morphological findings:	2000 mg/kg: gas accumulation in the gastro-intestinal tract. 2800 mg/kg: red discolouration of the glandular stomach; duodenum, small intestine and cervical lymph nodes; small haemorrhages or petechiae in the thymus. 3750 mg/kg: red discolouration of the duodenum; small intestine and glandular stomach; small haemorrhages in the stomach; petechiae in the thymus. 5000 mg/kg: purple discolouration of the small intestine, small haemorrhages in the thymus and some haemorrhages in the glandular stomach.
LD_{50}:	3329 mg/kg; 95% confidence interval: 2699 – 4179 mg/kg.
Result:	The notified chemical was of very low acute oral toxicity to the rat.

9.1.2 Dermal Toxicity (RCC-NOTOX 1989c)

Species/strain:	Rat/Wistar
Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	A single, 24-hour semi occluded application of neat test substance to intact skin at a dose of 2000 mg/kg in a dose volume of 2.21 mL/kg.
Test method:	OECD TG 402
Mortality:	One female died 5½ hours following start of treatment after showing absence of reaction.
Clinical observations:	Lethargy was observed in two animals during the treatment period.
Dermal response:	The treated skin surface of animals showed no irritation.
Morphological findings:	Macroscopic examination at necropsy of the animal found dead showed an enlarged stomach and superficial grey/white streaks on the liver. No gross macroscopic abnormalities were observed in surviving animals at termination.
LD_{50}:	> 2000 mg/kg bw.
Result:	The notified chemical was of low dermal toxicity to the rat.

9.1.3 Inhalation Toxicity (The Toxicology Research Laboratory 1990)

Species/strain:	Rat/Fischer 344
Number/sex of animals:	5/sex/group
Observation period:	14 days
Test method:	OECD TG 403; EC Method B2
Method of administration:	A single 4-hour, whole-body exposure to test substance vapour under dynamic exposure conditions at a flow rate of 30 L/minute.

Atmosphere Concentration:
Nominal 792 ppm (maximum attainable concentration);
Mean achieved atmosphere concentration, 694 ppm TWA (because of analytical malfunction this value is the TWA for the first 142 minutes);

Mortality Nil

Clinical observations: Transient perineal soiling in 2 female rats was observed on the day of exposure. Bodyweights of male and female rats were decreased (1-4%) on test day 2 but were comparable to pre exposure values by test day 4 in males or test day 8 in females.

Morphological findings: No abnormalities were detected at necropsy.

LC_{50}: > 792 ppm; >5.3 mg/L/4 hour

Result: The notified chemical was of low acute inhalation toxicity to the rat.

9.1.4 Skin Irritation (RCC-NOTOX 1989o)

Species/strain: Rabbit/New Zealand White

Number/sex of animals: 3 females.

Observation period: 3 days

Method of administration: A single 4 hour, semi occluded application of 0.5 mL of test substance to intact skin.

Test method: OECD TG 404; EC Method B4

Draize scores:

	Animal #		
Time after treatment (days)	***1***	***2***	***3***
Erythema			
1	1P	1P	1P
2	1	0	0
3	0S	0	0S
Oedema			
1	0	0	0
2	0	0	0
3	0	0	0

[a] see Attachment 1 for Draize scales. P - Irritation peripherally on exposed area. S – Scaliness.

Mean individual score (24, 48 & 72 hour observation):	Erythema/Eschar Formation: 0.67, 0.3, 0.3. Oedema: 0, 0, 0.
Comment:	The very slight erythema was reversible within 48 hours after exposure in two animals and within 72 hours in the third animal. No symptoms of systemic toxicity or mortality were observed.
Result:	The notified chemical was slightly irritating to rabbit skin.

9.1.5 Eye Irritation (RCC-NOTOX 1989d)

Species/strain:	Rabbit/New Zealand White
Number/sex of animals:	3 females
Observation period:	7 days
Method of administration:	A single instillation of 0.1 mL of the neat test substance into the conjunctival sac of the right eye of each rabbit. The left eye served as the control.
Test method:	OECD TG 405; EC Method B5

Draize scores of unirrigated eyes:

	Time after instillation														
Animal	***1 hour***			***24 hours***			***48 hours***			***72 hours***			***7 days***		
Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	1	2	0	3	1	1	2	1	0	1	1	0	0	0	0
2	1	2	0	2	1	1	2	1	0	1	1	0	0	0	0
3	1	2	0	2	1	0	1	0	0	1	0	0	0	0	0
Cornea	*All scores were zero*														
Iris	*All scores were zero*														

[1] see Attachment 1 for Draize scales. r = redness c = chemosis d = discharge.

Mean Individual scores (24, 48 and 72 hour observation):	Corneal opacity: 0, 0, 0. Iridial lesion: 0, 0, 0. Redness of conjunctivae: 2, 1.7, 1.3. Chemosis of conjunctivae: 1, 1, 0.3.
Ocular response:	Lacrimation was observed in all animals to day 3. There were no corneal or iridial effects. Adverse effects were observed in the conjunctivae resolving by day 7.
Result:	The notified chemical was slightly to moderately irritating to rabbit eye.

9.1.6.1 Skin Sensitisation (RCC-NOTOX 1990b)

Species/strain:	Guineapig/Dunkin-Hartley albino
Number of animals:	20 test, 10 control females
Test method:	OECD TG 406 Buehler Technique
Induction procedure:	Day 1 to 19: Test animals: 9 repeated occluded applications of 0.5 mL of neat test substance on days 1, 3, 5, 8, 10, 12, 15, 17 & 19; Control animals: as above, except for omitting the test substance.
Challenge procedure:	Day 29: Test and Control animals: A single, occluded application of 0.5 mL of diluted test substance (50% w/w in propylene glycol) and 0.5 mL vehicle alone. Grading of dermal responses occurred 24 and 48 hours post exposure.
Clinical observations:	No symptoms of systemic toxicity were observed during the study. One animal was unwell on day 29 and was sacrificed. At necropsy this animal showed firmed lungs, enlarged spleen and a white/yellow spot on the median liver lobe.

Number of Animals Exhibiting Grade 1 Responses (red spots, scattered reactions) Following Challenge:

	Test animals		***Control animals***	
Challenge concentration	***24 hours****	***48 hours****	***24 hours****	***48 hours****
50%	8/19	16/19	4/10	4/10

* time after patch removal.

Challenge outcome:	The testing facility considers grade 2 responses (moderate but confluent redness) as a sign of a positive skin reaction, provided that such reactions are not observed in the control group. None of the animals showed a grade 2 reaction in response to the 50% challenge concentration.
Result:	The notified chemical was non sensitising to guineapig skin.

9.1.6.2 Skin Sensitisation - (RCC-NOTOX 1991)

Species/strain:	Guineapig/Dunkin Hartley White
Number of animals:	Females, 20 test and 10 control
Test method:	OECD TG 406 Magnusson and Kligman Maximisation Method
Induction procedure:	Intradermal Induction: Test animals: Day 1: three pairs of intradermal injections (0.1 mL) into the dorsal skin of the scapular region: - Freund's complete adjuvant (FCA) 1:1 in distilled water; - the test substance, diluted to 2.5% w/v in arachis oil; - the test substance at 2.5% w/v emulsified in a 50:50 mixture of FCA and distilled water; Topical Induction: Day 7 – A 48-hour semi occluded application of 0.5 mL of neat test substance to the treated area; Control animals: Treated similarly to the test animals omitting the test substance from the intradermal injections and topical application
Challenge procedure:	Test and Control animals: Day 21: A 24 hour, occluded application of 50% w/w, 25% w/w, 10% w/w and 0% of test substance (0.05 mL) in propylene glycol, to each animal.

Number of Animals Exhibiting Grade 1 Responses Following Challenge:

Challenge concentration	***Test animals***		***Control animals***	
	24 hours*	***48 hours****	***24 hours****	***48 hours****
50%	0/20	4/20	0/10	0/10
25%	0/20	0/20	0/10	0/10
10%	0/20	0/20	0/10	0/10

* time after patch removal.

Challenge Outcome: The testing facility considers grade 1 responses (red spots, scattered reactions) as a sign of a positive skin reaction, provided that such reactions are not observed in the control group. A grade 1 response was observed in four test animals.

Result: The notified chemical was mildly sensitising to guineapig skin.

9.2 Repeated Dose Toxicity

9.2.1 28 Day Repeated Dose Oral Toxicity (Gavage) (RCC-NOTOX 1989b)

Species/strain: Rat/Sprague-Dawley

Number/sex of animals: Test and satellite animals: 5/sex/dose group

Study design: In a dose volume of 5 mL/kg rats received 0, 100, 400, or 1000 mg/kg/day by oral gavage for 28 consecutive days.
A satellite group was included for determination of red blood cell osmotic fragility as this effect has been observed with some other glycol ethers.

Test method: OECD TG 407; EC Method B7

Mortality Nil

Clinical observations:
There were no clinical signs of a reaction to treatment or behavioural change by treated rats in comparison with the controls. Growth in test animals was comparable to controls at all times.

Food intake of treated rats was similar to that of the controls. Observations on water consumption were not reported.

Clinical chemistry/Haematology
There were no differences of biological significance noted in blood chemistry parameters measured between control and treated rats. Minor statistically significant differences were within the range normally seen in rats of this age and strain.

No indication of haemolytic effects was noted *in vivo*. On *in vitro* exposure of erythrocytes to decreasing concentrations of saline solution, blood of females treated with the test substance showed an increase in osmotic fragility. This shift towards increased fragility was dose related. No difference in the osmotic fragility of treated males compared to controls was noted. No other statistically significant treatment related differences were observed.

Pathology:
No macroscopic observations were noted that were considered treatment related.

Statistically significant increases in the weights of liver and kidneys (after adjustment for body weight) were noted for males receiving 1000 mg/kg/day. Females at 400 and 1000 mg/kg had statistically significant increased liver weights when compared to controls, after adjustment for body weight (and before, for females receiving 1000 mg/kg/day). Statistically significant differences occurring between kidney weights of controls and females receiving 100 or 1000 mg/kg/day prior to adjustment of body weights were considered to be chance occurences. There were no differences in organ weights of rats receiving 100 mg/kg/day or males receiving 400 mg/kg/day when compared to controls considered of toxicological significance.

No microscopic observations were noted that were related to treatment with the test substance. Those that were observed are among those commonly found in rats of this age and strain.

Comment:
The observed liver weight increases in females receiving either 400 or 1000 mg/kg/day, occurred in the absence of changes in clinical chemistry or microscopic change, and is suggested to be due to increased metabolism. The toxicological significance of slight kidney weight increases observed in males at 1000 mg/kg/day is unknown as there were no corroborative changes in clinical chemistry or morphology. Separate, *in vitro*, examination of the blood of treated rats showed a tendency towards increased red blood cell fragility, but no evidence of *in vivo* haemolysis was noted during the course of the study.

Result:
Based on changes in kidney and liver weight the no observed adverse effect level (NOAEL) for this study is 100 mg/kg/day.

9.2.2 14-Day Palatability Study & 28-Day Repeated Dose Oral Toxicity (Drinking Water) (The Toxicology Research Laboratory 1992)

Species/strain:	Rat/Sprague-Dawley
Number/sex of animals:	5/sex/dose group/study
Study design:	Two separate studies were conducted, a 14-day palatability study and a 28-day toxicity study. Animals were exposed to 0, 100, 500, or 1000 mg/kg/day of test substance in drinking water for 14 or 28 consecutive days.

Test method: OECD TG 407; EC Method B7

Mortality Nil

Clinical observations:

14-day palatability study:

There were no in-life observations noted during daily examinations indicative of a treatment-related effect in rats at up to 1000 mg/kg/day. No ocular abnormalities were note during in-life observations.

Feed consumption was decreased by test day 3 in females at 1000 mg/kg/day and continued throughout the rest of the study. By test day 3, female rats at 1000 mg/kg/day had decreased water consumption values which persisted throughout the study. Body weights of females given the test substance at 1000 mg/kg/day were lower than the controls by 11% on test day 3 and continued to be lower than the controls for the remainder of the study.

Based on these results 1000 mg/kg/day was selected as the highest dose for the 28-day study with 500 and 100 mg/kg/day selected to evaluate a potential dose-response relationship.

28 day toxicity study:

There were no treatment-related observations during the study suggestive of systemic toxicity. No statistically identified treatment-related effects on mean body weights were noted in male or female rats at dose levels up to 1000 mg/kg/day. No treatment-related changes in feed consumption parameters were noted between control and treated rats. No treatment-related changes in water consumption were noted between animals of the control and 100 mg/kg/dose groups. The 500 and 1000 mg/kg/day dose groups had decreased water consumption rates: decreased by 10% by test day 3 in males; and decreased by 7% by test day 8 in females. The effect persisted in both sexes throughout the study.

Clinical chemistry/Haematology
Blood chemistry and haematology parameters were not investigated.

Pathology:
Statistically significant increases of 26% and 24% in absolute liver weights and 27% and 18% in relative liver weights of male and female rats respectively were observed in the 1000 mg/kg/day dose level.

Comment:
The results of the study substantiate drinking water as an acceptable route of administration for the assessment of systemic toxicity by confirming the liver weight increases noted at comparable dose levels in the studies conducted via gavage and inhalation (Sections 9.2.1 and 9.2.4 respectively). Decreased water consumption is assumed to reflect palatability, and under the conditions of this study, the NOAEL for palatability is 500 mg/kg/day.

Result:

Based on liver weight increases at 1000 mg/kg/day the NOAEL for this 28 day drinking water study is 500 mg/kg/day.

9.2.3 2-Week Repeated Dose Inhalation Toxicity (The Toxicology Research Laboratory 1991)

Species/strain:	Rat/Fischer 344
Number/sex of animals:	5/sex/dose group
Study design:	Whole body exposure to test substance vapour at 0, 70, 225, or 700 ppm (nominal) (0.465, 1.496, 4.654 mg/L) for 6 hours per day, 5 days per week for 9 exposures over a 11 day period, under dynamic exposure conditions at a flow rate of 30 L/minute. Mean achieved atmosphere concentration: 0, 68, 234, 699 ppm (0.452, 1.559, 4.647 mg/L).
Test method:	OECD TG 407; EC Method B7
Mortality	Nil

Clinical observations:
There were no in-life observations of note for either sex. A corneal opacity, a common observation in Fischer 344 rats, was observed in one female control rat post-exposure. There were no exposure-related effects on male or female body weights.

Clinical chemistry/Haematology/Urinalysis
There were no exposure-related effects in any haematological parameter. There were no exposure-related effects on any of the measured urinalysis parameters.

There was significantly decreased mean alkaline phosphatase (AP) activity and significantly increased mean blood albumin in both male and female rats at 700 ppm. The control group AP values for both sexes were at the upper end of the historical range for AP activity. The AP value for both male and female rats exposed to 700 ppm were also within the historical control range. Albumin values for both male and female rats exposed to 700 ppm were within or in slight excess of historical values.

Pathology:
Terminal body weights remained unaffected by treatment for all animals. Significantly increased absolute and relative adrenal weights were observed at 700 ppm. These adrenal weights were within or in slight excess of the test facility's historical values for this parameter. Significantly increased absolute liver weights were observed in males at 700 ppm and in females at 225 and 700 ppm. Relative liver weights were increased in a dose-responsive manner; significantly in both males and female at 225 and 700 ppm. Although there was no histopathological or other evidence of hepatic toxicity, the increased liver weights were considered to be treatment-related, possibly reflecting a physiological adaptation. There were no gross lesions attributable to test substance exposure.

Histopathologic changes related to administration were limited to the kidneys of male rats. The kidney lesion was characterised as a protein droplet nephropathy (PDN) and affected males at 225

and 700 ppm. With increasing vapor concentration the proportion of renal tubules with protein droplets increased and a slight increase in single cell death and mitotic figures were observed. At 225 ppm one male was graded 'very slight' while four males were graded as 'slight' PDN. At 700 ppm, PDN was 'slight' in three of the five male rats and 'moderate' (involving approximately 50% of the cortex) in the remaining two males.

The remaining histopathologic observations in treated rats were attributed to spontaneous disease processes commonly seen in rats of this strain and age and were not interpreted by the study authors to be treatment related.

Comments:
Kidney lesions, characterised as PDN, were present in male rats exposed to vapour concentrations of 225 or 700 ppm. Increased adrenal weights were observed at 700 ppm and increased liver weights at 225 and 700 ppm.

Result:
Based on changes in the kidneys and liver at 225 and 700 ppm the NOAEL for this study is 70 ppm (0.465 mg/L).

9.2.4 13-week Repeated Dose Inhalation Toxicity (The Toxicology Research Laboratory 1994a)

Species/strain:	Rat/Fischer 344
Number/sex of animals:	Study Group A: 10/sex/concentration; Study Group B: 10/sex/concentration; Study Group C: 10 males, 5 females.
Study design:	All animals received whole body exposure to vapourised test substance (nominal), under dynamic airflow conditions at a flow rate of 450 L/minute, as follows: Group A: 0, 50, 100 or 700 ppm (0, 0.332, 0.665, 4.654 mg/L) for 6 hours/day, 5 days/week for 13 weeks; Group B: 0 or 700 ppm for 6 hours/day, 5 days/week for 13 weeks followed by a 4 week recovery (treatment free) period; Group C: 0 or 700 ppm either for 4 weeks (5 rats/sex/concentration) or for 13 weeks (5 male rats/concentration). Achieved atmosphere concentration: 0, 52, 102, 707 ppm.
Test method:	OECD TG 407; EC Method B7
Mortality	Nil

Clinical observations:
All females at 700 ppm showed signs of un-coordination on the first day of exposure. Thereafter, no further observations of this type were noted. Males were unaffected by the treatment. No ophthalmologic abnormalities were noted in any study animal. Several other observations were made during the course of the study that were common in this age and strain of rat and not considered related to test substance exposure.

Body weights of males exposed to 100 or 700 ppm were elevated above control weights throughout most of the study but were only significantly different from controls on day 27. At 700 ppm, male rat body weights were significantly increased over controls during the recovery period. There were no treatment-related effects on female body weights.

Clinical chemistry/Haematology/Urinalysis:
AP activities in both sexes were significantly decreased after 13 weeks exposure to 700 ppm as well as after four weeks of recovery but were within the historical control range of the testing facility. The biological significance of this finding is uncertain as in pathological conditions, an increase, not decrease in AP activity is expected. A slight but significant increase in mean cholesterol was noted in females at 700 ppm. This finding was within the historical control range of the testing facility. Recovery females at 700 ppm and control females had identical mean values for cholesterol. Very slight but significant increases in total protein and albumin were noted in females at 700 ppm and this was attributed to biological variation.

There were very slight but significant decreases in red blood cell count, haemoglobin, and haematocrit in male rats at 700 ppm necropsied at 13 weeks. Significant, very slight decreases in haemoglobin and haematocrit were also observed in recovery males at 700 ppm. There was no supporting evidence of haemolysis or an effect on the bone marrow based on in-life observations, urinalysis and histopathology.

Urinalysis revealed significantly decreased specific gravity in both sexes at 700 ppm, which persisted in males after the recovery period. This finding is consistent with the histopathological finding of $\alpha_{2\mu}$-globulin nephropathy in male rats. For females, decreased specific gravity occurred in the absence of morphologic kidney changes and is attributable to biological variability but not considered biologically significant.

Pathology:
After 13 weeks, the absolute liver and testes weights of male rats at 700 ppm were significantly increased; relative liver weights were significantly increased at 100 and 700 ppm. After the recovery period, the final body weights of males at 700 ppm was significantly increased as were the absolute kidney, liver, testes and relative liver weights. In female rats at 700 ppm, absolute and relative liver, kidney and adrenal weights were significantly increased. Female rats at 100 ppm had significantly increased absolute and relative kidney weights. After the recovery period, rats at 700 ppm had significantly increased absolute and relative liver weights.

Microscopic examination of rats necropsied after 13 weeks identified the liver in both sexes and the kidney and adrenals in males as target organs.
Liver - centrilobular hypertrophy was evident in 35% of male and female rats at 100 ppm and 90% of both sexes at 700 ppm. The morphological finding in these groups correlated with significant liver weight increases in males at 100 ppm and both sexes at 700 ppm. These changes are considered physiologically adaptive. Centrilobular activity was not detected in livers of recovery group rats at 700 ppm; but increased liver weights persisted in both sexes.

Adrenal Gland – there was a slight increase in vacuolation of the zona fasciculata in males at 700 ppm. At 0, 50, 100, and 700 ppm the incidence of vacuolation in males was 0%, 0%, 10% and 60%, respectively. In recovery group males, the control and 700 ppm group incidences were 0% and 20%, respectively.
Kidney – in male rats at 100 ppm and 700 ppm, findings of protein droplet nephropathy (PDN) (graded as very slight) was observed, which consisted of an increased portion of the renal cortex with protein droplet containing tubules, a very slight increase in nuclear pleomorphism, occasional mitotic figures and occasional pyknotic or necrotic cells. The incidence of PDN was 0%, 0%, 40% and 90% at 0, 50, 100 and 700 ppm, respectively. The increased nuclear pleomorphism persisted in recovery males at 700 ppm.
$\alpha_{2\mu}$-globulin staining – there were no degenerative changes and no specific immunohistochemical $\alpha_{2\mu}$-globulin staining in the kidneys of females at 700 ppm after 4 weeks. At 4 weeks control males showed $\alpha_{2\mu}$-globulin staining in 20-25% of the renal cortex while males at 700 ppm had staining in 30-40% of the cortex. At 13 weeks only males were tested. Results were similar, but staining was slightly increased in both controls and treated rats compared with the 4-week time interval. In males there was a slight increase in staining. Control males had 25-30% staining while male rats at 700 ppm had 35-45% $\alpha_{2\mu}$-globulin specific staining of the renal cortex.

Comment:
Histopathologic changes were observed in the kidneys of male rats exposed to 100 and 700 ppm. The kidney lesion was characterised as a male rat specific, $\alpha_{2\mu}$-globulin-mediated, PDN. Increased liver weight and centrilobular hepatic hypertrophy were observed in both sexes exposed to 100 and 700 ppm. The morphologic changes in the liver appeared to be reversible, however, the liver weights remained elevated above controls after the 4-week recovery period. All of the liver changes were considered as consistent with physiologically adaptive responses (metabolic induction) to test substance exposure. The adrenal glands of male rats exposed to 700 ppm had slightly increased cortical vacuolation that was partially reversed during the 4-week recovery period (incidence of this finding decreased to 20%).

Result:
Based on changes in the kidneys and liver at 100 and 700 ppm the NOAEL for this study is 50 ppm (0.332 mg/L/6 hours).

9.3 Developmental and Reproduction Studies

9.3.1 Developmental Probe Study – Oral (Gavage) (CIVO 1990b)

Species/strain:	Rabbit/New Zealand White
Number/sex of animals:	32 females; at least 6 animals per dose group.
Test method:	Not stated; range finding study for developmental study see Section 9.3.2
Study design:	Animals were artificially inseminated and dosed orally by gavage at 0, 30, 100, 300, 500 mg/kg/day of test substance in water on day 6 through to day 18 of gestation. All animals were sacrificed on day 19.
Mortality	One of six animals at 300 mg/kg group died on day 10 after dosing and three of seven animals at 500 mg/kg also died after dosing (one on day 6 and two on day 13).

Clinical observations:
All females at 500 mg/kg/day showed lethargy after dosing and food and water intake was decreased. The decedent at 300 mg/kg/day also showed lethargy after dosing on day 10. Mean maternal body weight was decreased after the first six days of treatment.

Reproduction findings:
From the 32 inseminated females, 29 were pregnant. The fertility index ranged from 83% (300 mg/kg) to 100% (30 & 100 mg/kg). The mean numbers of corpora lutea and implantation sites were similar between test and control animals. No statistically significant differences were observed in the pre- and post-implantation loss, mean number of resorptions and live and dead foetuses. No significant differences were observed in the mean pregnant and empty uterus weight and the mean ovary weight.

Macroscopy of does:
Two animals at 500 mg/kg/day group and one at 300 mg/kg/day presumably died from lung collapse or pulmonary haemorrhage. Two of these animals also showed lesions in the pyloric region of the stomach or of the duodenum. The cause of death of the third animal at 500 mg/kg/day on day 6 is not known. This animal showed severe obstipation and urinary bladder distension. Mean liver weights relative to bodyweights were similar in all dose groups. The remaining changes observed in this study were randomly distributed over the test and control groups.

Macroscopy of foetuses:
Macroscopically visible differences (dysmature appearance and umbilical hernia) observed were comparable between treated and control groups.

Comment:
Treatment related mortality, lethargy and decreased mean maternal body weight were observed at 300 and 500 mg/kg/day.

Results:

The NOAEL for maternal toxicity is 100 mg/kg/day based on clinical signs of toxicity at 300 mg/kg/day and above. The NOAEL for foetal effects is 500 mg/kg/day.

9.3.2 Developmental Study - Oral (Gavage) (CIVO 1990a)

Species/strain:	Rabbit/New Zealand White
Number/sex of animals:	80 females, 20/dose group
Test method:	OECD TG 414; EC test Method B31

Study design:
Animals were artificially inseminated and dosed orally by gavage at 0, 25, 100, 250 mg/kg/day of test substance in water on day 6 through to day 18 of gestation. All animals were sacrificed on day 29.

Mortality:
25 mg/kg/day – one animal died on day 6 after dosing, and one died on day 16 before dosing;
100 mg/kg/day - one animal died on day 15 before dosing;
250 mg/kg/day – three animals died, one each on days 7, 8 and 18.

Clinical observations:
Treatment related signs of lethargy shortly after dosing were observed in two, four and six animals at 25, 100 and 250 mg/kg/day, respectively, reaching statistical significance at the highest dose. Dyspnoea, laboured breathing, retching, diarrhoea and conjunctivitis occurred in one or two animals or did not show any dose response relationship. Bodyweight and food and water intake were unremarkable.

Reproduction findings:
From the 80 inseminated females 67 were pregnant. The fertility index ranged from 75% (25 mg/kg/day) to 90% (0 mg/kg/day). One female at 25 mg/kg/day aborted. The mean numbers of corpora lutea and implantation sites were similar between test and control animals. In control animals, post-implantation loss was relatively high when compared to test animals. No significant differences were observed in the mean pregnant and empty uterus weight, the mean ovary weight, placenta and foetus weights and foetus length. The mean number of live and dead foetuses per litter, as well as the sex ratio did not reveal any treatment related effects.

Macroscopy of does:
In-study decedents demonstrated gross changes of the lungs (haemorrhages, dark spots, foamy fluid), the oral cavity (foamy fluid), trachea/bronchi (haemorrhagic fluid), which are considered to be related to a direct contact of the test substance with tissues of the respiratory tract, either by oesophageal reflux or evaporation of the test substance during dosing, or as a result of a dosing error. One animal at 250 mg/kg/day showed only dark red spots in the lung.

Mean liver weights, both absolute and relative to body weight were similar in all groups.

Foetal examination

Soft tissue

Visceral malformations were observed in four foetuses of three litters in the control group, two foetuses of two litters at 25 mg/kg/day, two foetuses of two litters at 100 mg/kg/day and four foetuses of two litters at 250 mg/kg/day.

0 mg/kg/day - A malformed head was observed in one foetus, featuring agnatia, cleft upper lip, malformed palate and tongue and malposition of the ears. In two foetuses from different litters the artery subclavia was missing. One of these foetuses also showed a dilated pulmonary artery.

25 mg/kg/day – One foetus had a dilated pulmonary artery. A foetus from a different litter showed an umbilical hernia.

100 mg/kg/day – A double aortic arch and a missing septum was observed in one foetus. A foetus from different litter showed atrophy of the right ovary.

250 mg/kg/day – One foetus showed agenesis of the spleen. Agenesis of the kidney, accompanied by agenesis of the ureter was observed in two littermates. A foetus from another litter showed malformations of the circulatory system and the heart.

All visceral malformations that were observed occurred in one or two foetuses. None of the observed visceral malformations were considered to be related to treatment.

Minor visceral anomalies and visceral variants were either observed in a number of foetuses in all groups or occurred only occasionally in one or a few foetuses.

Skeleton

Skeletal malformations were observed in two foetuses at 0 mg/kg/day and two foetuses at 250 mg/kg/day.

0 mg/kg/day - A complexity of malformations, scoliosis accompanied by reduced, dislocated and/or irregular shaped ribs and a bifurcated rib was observed in one foetus of one litter. In a foetus of another litter, fused, irregular ossified ribs accompanied by reduced, dislocated and irregular shaped thoracic vertebrae were observed.

250 mg/kg/day - Misshapen sternebrae were observed in one foetus. A complexity of malformations consisting of scoliosis accompanied by bifurcated ribs, fused and irregular shaped thoracic vertebrae were observed in one foetus of another litter. No skeletal malformations were observed that could be related to treatment. The number of foetuses with a 13^{th} rib, bilateral, was slightly, but signficantly increased at 250 mg/kg/day when compared to the control.

Minor skeletal anomalies and skeletal variants were observed in similar numbers of foetuses at 0 mg/kg/day and 250 mg/kg/day. No difference in ossification between foetuses at 0 mg/kg/day and 250 mg/kg/day was observed.

Placenta
Cysts were observed in 11 placentas of 8 litters at 0 mg/kg/day, one placenta of one litter at 100 mg/kg/day and five placentas of four litters at 250 mg/kg/day. One placenta at 0 mg/kg/day showed hypertrophy and another placenta a small haemorrhage.

Comments:
In all dose groups transient signs of lethargy was dose related reaching significance at 250 mg/kg/day. Mortality, except for one animal at 250 mg/kg/day, was related to dosing procedure rather than a systemic effect of the test substance. The one abortion was considered an incidental finding. No skeletal or visceral malformations, or anomalies were observed that could be related to the treatment with the test substance. A slight, statistically significant increased incidence of foetuses with extra rudimentary rib was observed at 250 mg/kg/day, the dose which caused maternal toxicity and death.

Results:
The NOAEL determined for maternal toxicity is 100 mg/kg/day based on clinical signs at 250 mg/kg/day. The NOAEL determined for developmental effects is 250 mg/kg/day.

9.3.3 Developmental Study – Vapour Inhalation (The Toxicology Research Laboratory 1994a)

Species/strain:	Rat/Sprague-Dawley
Number/sex of animals:	120 females
Test method:	OECD TG 414; EC Method B31

Study design:
Groups of 30 bred females were exposed to nominal concentrations of 0, 70, 225, 700 ppm (0, 0.465, 1.496, 4.654 mg/L) of test substance vapour for 6 hours/day on days 6 through to day 15 of gestation. All animals were sacrificed on day 21. The achieved vapour concentrations were: 0, 71, 224, 702 ppm.

Mortality:
Nil.

Clinical observations:
A slight decrease in feed consumption, a corresponding decrease in body weight gain at the start of the exposure period and an increase in absolute and relative weights of dams at 700 ppm were the only treatment related maternal effects observed.

Reproduction findings:
There were no abortions. There were no treatment related effects on the pregnancy rate, number of corpora lutea, number of implantations, preimplantation loss, resorptions, litter size, number of dead foetuses, foetal sex ratio, foetal body weight or gravid uterine weight at any exposure concentration.

Macroscopy of dams:
The absolute and relative liver weights were significantly increased at 700 ppm and this finding was considered treatment related.

Foetal examination
Malformations were detected in three foetuses, one each at 0 ppm, 70 ppm, and 700 ppm. Microphthalmia was noted in one each at 0 ppm and 700 ppm. Thinning of the abdominal wall tetrabrachia and tetracurra occurred in one foetus at 700 ppm. The incidence of malformations was reported to be within the historical control of the testing facility and not considered treatment related.

Effects suggestive of delayed maturation (foetotoxicity) were exhibited as statistically significant increases in the incidence of delayed ossification of the cervical centra and bones of the skull at 700 ppm.

Comments:
Treatment related maternal toxicity (decreased bodyweights and feed consumption) were observed at 700 ppm. Delays in ossification in foetuses occurred at the concentration causing maternal toxicity. No maternal toxicity or developmental effects were observed at 70 or 225 ppm.

Results:
The NOAEL determined for both maternal toxicity and developmental effects is 225 ppm (1.496 mg/L/6-hours).

9.3.4 Two Generation Reproduction Study – Drinking Water (The Toxicology Research Laboratory 1994b)

Species/strain:	Rat/Sprague-Dawley
Number/sex of animals:	30/sex/dose
Test method:	OECD TG 416; EC Method B35.
Study design:	Groups of 30 females and males were administered drinking water that provided 0, 50, 250, 1000 mg/kg/day, 7 days/week for two generations. Following 11 weeks of exposure, the P1 adults were mated to produce the F1 litters. After weaning, 30 pups/sex/dose were selected to become P2 adults. An additional pair fed/watered (PF) control group was added to the study at the start of the 12 week P2 premating period in order to control for palatability effects observed in the P1 adults. Following 12 weeks of exposure, the P2 and PF adults were mated to produce the F2 litters.

Mortality	P1 Adults – Two females at 50 mg/kg/day, one on gestation day 23 and the other on lactation day 11. P2 Adults – One male at 0 mg/kg/day was sacrificed on day 29. One female at 50 mg/kg/day on day 2 of lactation. One female at 1000 mg/kg/day was sacrificed on lactation day 2.

Reproductive findings:
No treatment related effects were observed in male or female fertility indices, time to mating, pup sex ratio or litter size in P1 adults and F1 litters in any dose group. No treatment related effects were observed in male or female fertility indices, time to mating, or pup sex ratio in P2 adults and F2 litters in any dose group.

P1 & P2 findings
No treatment related effects on behaviour or demeanour were observed in either sex at any dose. During the study animals were treated for pinworm.

Exposure of adult male and female rats to 250 and 1000 mg/kg/day of the test substance resulted in treatment-related effects in both parental generations (P1 and P2). These effects included decreased water consumption, which resulted in secondary effects on feed consumption and body weight, as well as increased absolute and relative kidney and liver weights.

Histologic effects occurred in the liver of adult male or female rats at 250 or 1000 mg/kg/day. These effects consisted of a dose-related increased hepatocyte size (considered to be physiologic adaptation) and was consistent over the P1 and P2 generations. Additionally, two minor lesions possibly related to treatment were present in livers of a few P2 males at 1000 mg/kg/day. These lesions were small foci of hepatocyte necrosis (7 test vs 2 controls); and bile duct hyperplasia (9 test vs 3 controls). Kidney lesions were present in male rats only. Increased hyaline protein droplets in the proximal tubular epithelium was present in slightly less than half of males at 1000 mg/kg/day and one third of males at 250 mg/kg/day in each parental generation. The protein was identified as $\alpha_{2\mu}$-globulin by special staining. A slightly higher incidence of the "slight" grade of a spontaneous renal lesion termed tubule "degeneration with regeneration" was noted in P1 males at 1000 mg/kg/day. This finding was not observed in P2 males. No other histopathological lesions were attributed to ingestion of the test substance.

F1 & F2 findings:
Parental effects observed at 1000 mg/kg/day were accompanied by neonatal effects in the F1 and F2 litters. F1 and F2 pups from dams at 1000 mg/kg/day exhibited decreased survival early in the lactation period. Decreases were observed in the average bodyweight of male and female F1 pups from dams given 1000 mg/kg/day. The average weight of F2 pups was slightly increased in 1000 mg/kg/day litters and was inconsistent with F1 results. However, this increase was consistent with a decrease in the average number of F2 pups born at 1000 mg/kg/day when compared to control litters. Pup bodyweights of both groups were comparable at the end of the P2 lactation period suggesting that neonatal growth of the F2 1000 mg/kg/day pups may have been slightly retarded, consistent with decreased survival at this dose level. The effects observed on F1 pup bodyweight and F1 and F2 survival were attributed to treatment as the bodyweights and survival of pups from the pair fed/watered control group were not affected by the feed and water restriction.
In study decedents:
The deaths of the two P1 dams at 50 mg/kg/day was not considered treatment related. The P2 dam at 50 mg/kg/day was observed as having dystocia and had delivered five live pups and one dead pup

prior to death. At necroscopy, 11 pups remained in the uterus. The P2 dam at 1000 mg/kg/day was sacrificed in moribund condition after delivering three dead pups. This dam was observed to have dystocia and decreased activity. At necroscopy, a foetus was found lodged in the cervix and 16 dead foetuses remained in the uterus.

Comments:
Treatment related histopathological effects and weight increases occurred in the kidneys and liver at 250 or 1000 mg/kg/day in both parental generations. Decreased survival early in the lactation period and bodyweight decreases in F1 pups at 1000 mg/kg/day were attributable to treatment. Reproductive parameters were not affected by treatment.

Results
The parental NOAEL for systemic effects was 50 mg/kg/day. The NOAEL for reproductive toxicity is 1000 mg/kg/day. The NOAEL for neonatal toxicity was 250 mg/kg/day.

9.4 Genotoxicity

9.4.1 *Salmonella typhimurium* Reverse Mutation Assay (Health and Environmental Services 1989b)

Strains:	*Salmonella typhimurium*: TA 98, TA 100, TA 1535, TA 1537
Metabolic activation:	Liver homogenate from Sprague-Dawley male rats pre treated with Aroclor 1254 at 500 mg/kg bodyweight
Experimental design Concentrations:	Two independent experiments were conducted with each of the following concentrations tested in triplicate, both in the presence and absence of metabolic activation: 0, 5.0, 16.67, 50.0, 166.7, 500, 1 666.7, 5 000 μg/plate. The test substance was dissolved in water. Appropriate strain specific controls were tested.
Test method:	OECD TG 471
Comment:	No toxicity was observed. Precipitation was noted at and above 1 500 μg/plate; There was no increase in the number of revertant colonies above the control, or demonstration of a dose response relationship, either in the presence or absence of metabolic activation at any test concentration. The positive control substances all produced marked increases in the frequency of revertant colonies and the activity of the S9 fraction was found to be satisfactory.
Result:	The notified chemical was non mutagenic under the conditions of the test.

9.4.2 Forward Mutation Assay (The Toxicology Research Laboratory 1994c)

Cells:	Chinese Hamster Ovary (CHO),
Metabolic activation system:	Liver fraction (S9) from rats pre treated with Aroclor 1254 (500 mg/kg)
Dosing schedule:	Two independent experiments were conducted at the following concentrations in triplicate in the presence or absence of S9. The exposure period was 4 hours. Experiment 1 Cultures were treated at 0, 312, 625, 1250, 2500, or 5000 µg/mL. Experiment 2 Cultures were treated at 0, 1000, 2000, 3000, 4000, or 5000 µg/mL.
Test method:	OECD TG 476 CHO cells, HGPRT locus; EC Method B17
Comment:	No cytotoxicity was observed in Experiment 1. In both experiments the test substance did not cause any significant increases in the incidence of mutant colonies in the presence or absence of metabolic activation from that of the negative control. Positive controls used in the test caused marked increases in the incidence of mutant colonies and the activity of the S9 fraction was found to be satisfactory.
Result:	The notified chemical did not induce gene mutations in CHO cells.

9.4.3 Chromosomal Aberration Assay (Health and Environmental Services 1989a)

Cells:	Rat lymphocytes
Auxillary Metabolic activat system:	Liver S9 fraction from Sprague-Dawley rats pre treated with Aroclor 1254 at 500 mg/kg.
Dosing schedule:	Each concentration was tested in duplicate, in two independent experiments for a treatment time of 4 hours in the presence or absence of metabolic activation at test concentrations of 0, 166.7, 500*, 1666.7*, 5000* µg/mL. Appropriate clastogenic control substances were used. *cultures selected for metaphase analysis.
Test method:	OECD TG 473; EC Method B10.
Comment:	Cytotoxicity was not observed at any concentration. The test substance did not cause any significant increases in the

incidence of cells with chromosomal aberrations, polyploidy or endoreplication, at the concentrations analysed in the presence or absence of metabolic activation.
Positive controls used in the test caused marked increases in the incidence of aberrant cells and the activity of the S9 fraction was found to be satisfactory.

Result: The notified chemical was not considered clastogenic under the conditions of the test.

9.4.4 Micronucleus Assay in the Bone Marrow Cells of the Mouse (Health and Environmental Services 1992)

Species/strain: Mouse/CD-1 (ICR) BR

Number and sex of animals: 5/sex/test group

Study design: Test substance: 0, 200, 666, 2000 mg/kg.
Positive control, cyclophosphamide (CP): 120 mg/kg.
Vehicle control: corn oil.
Groups of 10 animals given the test substance or corn oil were sacrificed 24, 48 or 72 hours after treatment. Animals given CP were sacrificed 24 hours after treatment.
All doses of test substance and CP were administered by oral gavage.

Test method: OECD TG 474; EC Method B12

Comment: 1000 polychromatic erythrocytes (PCE) were counted.
There was no significant increase in micronucleated PCE caused by the test substance at any sampling time. The ratio of PCE to monochromatic erythrocytes (PCE/NCE) for each group was similar to the control group.
The positive control caused a significant increase in micronucleated PCE.

Result: The notified chemical did not induce a significant increase in micronucleated PCE in bone marrow cells of the mouse *in vivo.*

9.5 Pharmacokinetic Studies

9.5.1 Pharmacokinetic Studies – *in vivo* (The Toxicology Research Laboratory 1993)

Species/strain: Rat/Sprague-Dawley

Study design:

Five experiments were conducted:

I) Low dose oral absorption, distribution, metabolism and excretion (ADME):

A single oral gavage nominal dose of 30 mg/kg ^{14}C-test substance dissolved in distilled water in a dose volume of 2 mL/kg to five rats of each sex. Urine, faeces, expired organics and $^{14}CO_2$ were collected at intervals before sacrifice at 72 hours post dosing. At sacrifice the carcass and skin were homogenised.

II) High dose oral ADME:

A single oral gavage nominal dose of 1000 mg/kg ^{14}C-test substance dissolved in distilled water in a dose volume of approximately 4 mL/kg to five male rats. As above, excreta were collected.

III) Low dose oral blood level:

A single oral gavage nominal dose of 30 mg/kg ^{14}C-test substance dissolved in distilled water in a dose volume of 2 mL/kg to five male rats. Blood was sampled from the jugular vein at 0.08, 0.25, 0.50, 1.0, 1.5, 3.0, and 6.0 hours post-dosing.

IV) Low dose oral tissue distribution:

A single oral gavage nominal dose of 30 mg/kg ^{14}C-test substance dissolved in distilled water in a dose volume of approximately 2 mL/kg to five male rats. Animals were sacrificed 1.5 hours post-dosing. Blood, liver, kidney, adrenal glands, fat, brain and muscle tissue were collected.

V) Multiple low dose oral ADME:

A single oral gavage nominal dose of 30 mg/kg unlabelled test substance dissolved in distilled water in a dose volume of approximately 2 mL/kg to five male rats for six consecutive days. On the seventh day 30 mg/kg ^{14}C-test substance was administered. Urine, faeces, and $^{14}CO_2$ were collected at intervals before sacrifice at 72 hours post dosing. At sacrifice the carcass and skin were homogenised.

Results:
Virtually all the test substance administered by gavage was absorbed and subsequently metabolised before elimination. Absorption was rapid. Mean radioactivity levels in blood approached peak levels from 15 minutes post dosing until 90 minutes post dosing. Levels of radioactivity in rapidly perfused tissues (liver and kidney) and slowly perfused tissues did not exceed the level of radioactivity in the blood, suggesting that neither the test substance nor its metabolites preferentially concentrate in target tissues. The disposition of the test substance was very similar in male and female rats, and repeated administration of low doses (30 mg/kg) of the test substance did not affect

the disposition of a subsequent dose of 30 mg/kg of ^{14}C tagged test substance. The primary routes of elimination for radioactive metabolites were expired air (30 to 35% of administered radioactivity was recovered as $^{14}CO_2$) and urine (where 55 to 60% of the radioactivity was recovered in 10 to 12 chromatographically distinct species).

Disposition of the test substance in rats appeared to be dose dependent. Following administration of approximately 1000 mg/kg the rates of elimination of radioactivity were much slower than following administration of targeted 30 mg/kg. At 30 mg/kg/day, 80 to 85% of ^{14}C was eliminated within 12 hours. Whereas at 1000 mg/kg/day a greater proportion was eliminated in the 12 to 24 hour period.

The metabolic pathway which resulted in the presence of an alkoxy acid metabolite (exact identity of metabolite is exempt information), which is a developmental toxicant, in urine appeared to become more prominent at the higher doses of the test substance (4 to 5% of theoretical maximum yield after 30 mg/kg test substance versus 12.9% after 1000 mg/kg). Other metabolites were not identified. (Miller RR et al 1983) suggested that the toxicity of glycol ethers (this is known for 2-methoxy ethanol, 2-ethoxy ethanol and 2-butoxy ethanol) may be related to the production of alkoxy acids. This dose dependency in metabolism may have significant implications for extrapolating the toxicity of the test substance from high doses to low doses.

9.5.2 Metabolism of Propylene Glycol Ethers – *in vitro* (The Toxicology Research Laboratory 1995)

Species/strain:	Rabbit:	New Zealand White, female;
	Rat:	Fischer 344, female.

Study design:
An *in vitro* liver slice metabolism assay was used to investigate the formation of an alkoxy acid (exact identity of acid is exempt information), a supposed developmental toxicant, from six propylene glycol ethers including β-propylene glycol methyl ether (β-PGME) and the notified chemical. Formation of alkoxy acid by liver slices from both rat and rabbit liver was quantitatively determined for each substrate. Ethoxycoumarin – O - deethylase activity, a measure of microsomal mixed function oxidase activity, was assayed in representative slices for each experiment as an indication of metabolic capacity of the system.

Results:
Comparison of species differences in formation of the alkoxy acid from the propylene glycol ethers studied demonstrated that *in vitro* metabolism of β-PGME led to the formation of much greater amounts of the alkoxy acid (rabbit slices: 3- to 21-fold; rat slices: 62- to 170-fold) than any of the other propylene glycol ethers investigated. The calculated *in vitro* rate of the alkoxy acid formation for the notified chemical of 14 µg alkoxy acid/g liver/hour was in reasonable agreement with the *in vivo* rate of 7.3 µg alkoxy acid/g/liver/hour based on data reported in Section 9.5.1. This agreement indicated that the *in vitro* metabolism of the notified chemical to an alkoxy acid, quantified with the liver slice technique, was representative of *in vivo* formation of the alkoxy acid from the notified chemical.

In addition, these *in vitro* results suggest that the species difference in sensitivity to β-PGME induced developmental toxicity demonstrated *in vivo* between rat and rabbit, is not due to increased formation of the alkoxy acid by rabbit as compared to rat.

The study report depicted proposed metabolism schemes for two isomers of the notified chemical, the main isomer being metabolised to primary alcohols by mixed function oxidases, then oxidised in part to the alkoxy acid via alcohol/aldehyde dehydrogenases, whereas a minor isomer is first metabolised to secondary alcohols then a primary alcohol and a glycol.

9.6 Overall Assessment of Toxicological Data

Toxicokinetics
The kinetics of ^{14}C-labelled notified chemical has been characterised in rats following oral administration. Virtually all of the substance administered at dose levels ranging from 30 to 1000 mg/kg/day was rapidly absorbed and subsequently metabolised. Most of the substance was eliminated rapidly either in expired air as CO_2 (30 to 35%) or in urine (50 to 55%) as 10 to 12 chromatographically distinct species. Only one of the metabolites was identified, an alkoxy acid which is a known developmental toxicant. Repeated administration of 30 mg/kg/day did not affect the disposition or kinetics of the notified chemical although dose-dependent kinetics were suggested by the slower elimination of radioactivity at 1000 mg/kg/day versus 30 mg/kg/day. No tissues preferentially accumulated ^{14}C. The notified chemical was metabolised to the corresponding alkoxy acid via alcohol/aldehyde dehyrdogenases. However, this represented a minor route of metabolism for the notified chemical as only 4 to 5% of the dose at 30 mg/kg/day and 12.9% of the dose at 1000 mg/kg/day was eliminated as the alkoxy acid.

Acute Effects
An acute oral gavage toxicity study in Wistar rats determined the LD50 for both sexes to be ≥ 3300 mg/kg/day. A 4-hour vapour inhalation study was conducted in Fischer 344 rats at a nominal concentration of 792 ppm, the TWA analytical concentration during the first 142 minutes of the exposure was 694 ppm. There were no deaths. The LC50 was > 792 ppm (5.3 mg/L). Upon dermal application, lethargy was observed in two animals during the 24 hour treatment period. The dermal LD50 determined is > 2000 mg/kg/day.

The notified chemical is considered slightly irritating to rabbit skin and slightly to moderately irritating to rabbit eye. In guineapigs, the notified chemical was non-sensitising in a non-adjuvant study, but mildly sensitising in an adjuvant study (sensitisation response of 20%).

Considering a molecular weight of less than 500 and by analogy to other glycol ethers it is assumed that the notified chemical is readily absorbed through the skin. The notified chemical has solvent properties and prolonged or repeated skin contact may result in de-fatting of the skin

Repeat Dose Studies
Oral
In a 28-day toxicity study, male and female Sprague-Dawley (SD) rats received doses of 0, 100, 400 or 1000 mg/kg/day by gavage. Liver weight increases were observed in females at 400 or 1000 mg/kg/day; slight kidney weight increases were noted in males receiving 1000 mg/kg/day. The NOAEL for the study was 100 mg/kg/day.

A drinking water toxicity study was conducted in SD rats receiving 0, 100, 500 or 1000 mg/kg/day for 28 days. In life observations, body weights and feed consumption were not affected by treatment at any dose in males or females. Water consumption was slightly decreased in rats given 1000 mg/kg/day. No significant effects on liver weights were observed in animals given 100 or 500 mg/kg/day. Histopathologic evaluation of organs was not performed. The NOAEL for this study is 500 mg/kg/day based on significantly increased liver weights at 1000 mg/kg/day.

Inhalation
A two-week vapour inhalation study was conducted in Fischer 344 rats at concentrations of 0, 70, 225 or 700 ppm. In life observations, bodyweights, haematology, clinical chemistry and urinalysis parameters were all unaffected by treatment. No gross pathologic observations were made at necroscopy that were considered to be treatment related. Liver weights were significantly increased in males and females exposed to 225 and 700 ppm as were adrenal weights in both sexes exposed to 700 ppm. PDN was observed in kidneys of males exposed to 225 and 700 ppm. The NOAEL was 70 ppm (0.465 mg/L).

Inhalation exposure to vapours of the notified chemical at 0, 50, 100 or 700 ppm in Fischer 344 rats for 13 weeks caused increased liver weight and hypertrophy in both sexes at 100 and 700 ppm, and in male rats only $\alpha_{2\mu}$-globulin nephropathy was observed at 100 and 700 ppm, and slight adrenal cortical vacuolation at 700 ppm. The morphologic changes in the liver appeared to be reversible, however, the liver weights remained elevated above controls after the 4-week recovery period. All of the liver changes were considered by the study authors as consistent with physiologically adaptive responses to test substance exposure. The adrenal gland cortical vacuolation was partially reversed during the 4-week recovery period. The slight statistically significant decrease in erythrocyte count in male rats at 700 ppm were likely representative of biological variability as opposed to a direct haemotoxic effect of the notified chemical. Based on changes in the kidneys and liver at 100 and 700 ppm the NOAEL was 50 ppm (0.332 mg/L).

Concluding remarks – Following inhalation or oral exposure, the target organs of toxicity were the liver (weight increase, hypertrophy), kidney (weight increase, $\alpha_{2\mu}$-globulin nephropathy in male rats) and adrenals (weight increase, cortical vacuolation). These effects were mostly seen at high exposure levels that cause sedation. The liver and adrenal effects suggest adaptive responses and were reversible to some extent. The $\alpha_{2\mu}$-globulin nephropathy is a male rat specific effect.

Developmental Effects

Test	*Species*	*NOAEL*	
		Maternal toxicity	*Developmental effects*
Probe study, oral, gavage	Rabbit	100 mg/kg/day	500 mg/kg/day
Treatment related mortality, lethargy and decreased mean maternal body weight were observed at 300 and 500 mg/kg/day in does.			
Oral, gavage	Rabbit	100 mg/kg/day	250 mg/kg/day
In does at 250 mg/kg/day, there was one death (of unknown cause) and dose related lethargy. In foetuses of does at 250 mg/kg/day there was an increased incidence of extra rudimentary rib.			
Inhalation	Rat	225 ppm	225 ppm
Treatment related maternal toxicity (decreased bodyweights and feed consumption, increased liver weight) was observed at 700 ppm in dams. In foetuses, delayed ossification occurred at 700 ppm.			

Concluding remarks – By either the oral or inhalation route, developmental effects in foetuses were observed at concentrations that caused treatment related maternal toxicity.

Reproductive Effects

Test	*Species*	*NOAEL*		
		Parental, systemic effects	*Reproductive effects*	*Neonatal toxicity*
Oral, drinking water, 2-generation	Rat	50 mg/kg/day	1000 mg/kg/day	250 mg/kg/day

Treatment related weight increases and histopathological effects occurred in the kidneys (PDN) and liver (dose-related increased hepatocyte size, small foci of hepatocyte necrosis, bile duct hyperplasia) at 250 or 1000 mg/kg/day in both P1 and P2. Decreased survival early in the lactation period and bodyweight decreases in F1 pups at 1000 mg/kg/day. Reproductive parameters were not affected by treatment.

Concluding remarks – Parental effects observed at 1000 mg/kg/day were accompanied by neonatal effects in F1 and F2 litters.

Protein droplet nephropathy

The finding of PDN in the repeat dose and two-generation studies was limited to male rats only. Special staining of the protein droplets identified the presence of $\alpha_{2\mu}$-globulin. Some chemicals cause renal tumours in rats via a mechanism involving $\alpha_{2\mu}$-globulin nephropathy (for example, tert butyl alcohol). The notifier indicates that long term testing to investigate the formation of tumours is not planned.

Genotoxic Effects

The notified chemical was non mutagenic in a bacterial reverse mutation assay. In two *in vitro* studies, the notified chemical was non mutagenic in a mammalian gene mutation test on Chinese hamster ovary cells and non clastogenic in a chromosomal aberration assay using rat lymphocytes. *In vivo*, the notified chemical was not considered clastogenic in the mouse micronucleus test.

Hazard Classification

Based on the results of studies for the toxicological endpoints investigated, the notified chemical does not meet the Approved Criteria (NOHSC 1999) for classification as a hazardous substance.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

10.1 Summary of Ecotoxicity

Test	*Species*	*Results*
Acute Toxicity Static, Nominal (OECD TG 203)	Guppy (*Poecilia reticulata*)	LC50(96 h) > 1000 mg/L NOEC = 1000 mg/L
Prolonged Toxicity Flow-through (OECD TG 204)	Rainbow trout *(Oncorhychis mykiss)*	LC50(14 d) > 300 mg/L NOEC = 300 mg/L
Acute Immobilisation Semi-Static, Nominal (OECD TG 202)	Water flea (*Daphnia magna*)	LC50(24 h) > 1000 mg/L NOEC (24 h) = 320 mg/L LOEC (24 h) = 320 mg/L
Reproduction Test Semi-Static, Nominal (OECD TG 202B)	Water flea (*Daphnia magna*)	NOEC (21 d) = 10 mg/L LOEC (21 d) (mobility) = 32 mg/L LOEC (21 d) (reproduction) = 100 mg/L
Level of Phytotoxicity Static, Measured (OECD TG 201)	Green Alga (*Selenastrum capricornutum)*	<u>Cell Count/mL</u> EC50(72 h) = 4307 mg/L NOEL(72 h) = 60 mg/L EC50(96 h) = 7188 mg/L NOEL(96 h) = 0 mg/L EC50(120 h) = 8491 mg/L NOEL(120 h) = 1433 mg/L <u>Cell Volume</u> EC50(72 h) = 1746 mg/L NOEL(72 h) = 60 mg/L EC50(96 h) = 7602 mg/L NOEL(96 h) = 0 mg/L EC50(120 h) = 8344 mg/L NOEL(120 h) = 1433 mg/L
Acute Toxicity (OECD TG 207)	Earthworms *(Eisenia foetida foetida)*	LC50(14 d) > 1000 mg/kg dry soil NOEC = 1000 mg/kg
Terrestrial Plant Growth Static (OECD TG 208)	Oat *(Avena sativa: Wilma)*	LC50(17 d) > 100 mg/kg EC50(17 d) > 100 mg/kg NOEC = 100 mg/kg
	Chinese Cabbage (*Brassica campestris: Chinensis: Dalida*)	LC50(17 d) > 100 mg/kg EC50(17 d) > 100 mg/kg NOEC = 100 mg/kg
	Lettuce *(Latuca sativa: Pontiac)*	LC50(17 d) > 100 mg/kg EC50(17 d) > 10 mg/kg NOEC = 10 mg/kg

10.2 Fish

10.2.1 Guppy (RCC-NOTOX 1990a)

Based on the results of the range finding study, the guppies were only exposed to the one test concentration of 1000 mg/L. No significant mortality or any other effects were observed at either the nominally 1000 mg/L (891 mg/L measured) test solution or the blank control after 96 hour exposure. Therefore, the results indicate that the notified chemical is practically non-toxic to the guppy.

10.2.2 Rainbow trout (Environmental Toxicology & Chemistry Research Laboratory 1991b)

In the 14 day prolonged toxicity test rainbow trout were continuously exposed to 23, 38, 65, 110, 181 or 300 mg/L (measured) of the notified chemical. There was no mortality or any other effects at any concentration tested. Therefore, the results indicate that the notified chemical is practically non-toxic to the rainbow trout.

10.3 Daphnia RCC (RCC-NOTOX 1989a)

The water fleas were exposed to 100, 320, 560 or 1000 mg/L (nominal – not measured) of the notified chemical in the acute toxicity test. There was no mortality at any concentration tested. Therefore, the results indicate that the LC50 for the notified chemical is higher than 1000 mg/L. However, at 320 mg/L and higher daphnias were observed floating at the surface.

In the daphnia reproduction test, the test animals were exposed to 10, 32, 100, 320 or 1000 mg/L (plus control) of the notified chemical (measured) for 21 days (RCC-NOTOX 1992). The chemical was found to adversely influence the reproduction of daphnia at 100 mg/L and above by inducing high incidences of immobility and mortality among young of the first 2 broods and the parent animals. The young of later broods appeared to be much less sensitive, with the reproduction rate recovering to approximate that of the control, indicating a possible adaptation mechanism. The LOEC for reproduction was 100 mg/L but the LOEC for mobility (including parents and F1 generation) was 32 mg/L. Therefore, it is unlikely that the chemical will cause long-term adverse effects on *Daphnia magna*.

10.4 Algae (Environmental Toxicology & Chemistry Research Laboratory 1991a)

The algae test was conducted over a period of 5 days with aliquots being removed for cell counting after 72, 96 and 120 hours. The series of twelve measured concentrations of the test substance ranged from ~50 mg/L to ~1000 mg/L (plus control) with three replicates at each concentration. Each test vessel contained an initial algal cell density of 10 000 cells/mL. The results indicate that at no time from 72 to 120 hours was the chemical toxic to green algae as no inhibition occurred.

10.5 Earthworms RCC (RCC-Umweltchemie AG 1991)

The earthworm test was conducted in an artificial soil system with ten earthworms/group exposed to the notified chemical in soil of 62.5, 125, 250, 500 and 1000 mg/kg (plus control) (dry soil weight basis). There were four replicates per concentration. Chloracetamide was used as a reference compound and the LC50 values after 7 and 14 days were 30.0 and 29.1 mg/kg soil, respectively. After 7 and 14 days the test substance caused no mortality or abnormal symptoms at any concentration and no inhibitory effects on body weight were observed.

10.6 Plants (RCC-NOTOX 1993)

The plant growth test was conducted under static methodology with forty seeds of three species of plants (oats, cabbage, lettuce) exposed to 1.0, 10.0 and 100 mg/kg test chemical (plus a water control) for 17 days. There were four replicates/concentration. Under the conditions of the test, with the measured parameters being emergence and the early stage of growth, no toxicity was observed at any concentration in the oats or cabbage. The lettuce growth was 32% of the control at 100 mg/kg concentration. Effect on root growth was observed in all lettuce seedlings at 100 mg/kg. A reference test to check the sensitivity of the test systems using Aatisin (Schering, Aagrunol) (concentrations of 1.0, 10.0 and 100 mg/kg) was conducted and the NOEC values were 1.0 mg/kg for all three plant species.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The notified chemical will be imported and used as a solvent in cleaning products, floor coatings and chemiluminescent applications. Losses during formulation should be minimised, as the procedures are controlled batch processes in closed vessels, and will be collected and discharged to municipal or trade-waste sewers, or incinerated. Products of incineration will include water and oxides of carbon.

When the notified chemical is used as a component of a cleaning or paint stripping product, most of the chemical is likely to be discharged to sewer where it will be treated at the sewerage treatment plant before discharge via outfall to the aquatic environment. It is expected to pass through the treatment process largely unchanged as it is relatively slowly biodegraded, and highly soluble in water. The notifiers provided a scenario where 3.9 tons per annum (tpa) (calculated from the expected import volume and predicted fate) of the notified chemical is discharged to water (sewers) in the major metropolitan areas (Melbourne - 46% usage and Sydney – 54% usage). Discharge is estimated to occur on 230 days per annum (48 weeks x 5 excluding 10 public holidays) as the products containing the chemical are to be used almost solely by professional tradespersons.

- Malabar system (Sydney, NSW), for an average daily flow of 455 ML/day the quantity of the notified chemical = 0.54 x 3.9 = 2.145 tpa

$$PEC = \frac{(2.145 \times 10^9) \text{ mg per annum}}{(230 \text{ days/annum} \times 455 \times 10^6 \text{ L})}$$

$$= 0.0205 \text{ mg/L}$$

10:1 dilution on release to outfall = 2.1 μg/L.

- Werribee system (Melbourne, VIC), for an average daily flow of 470 ML/day the quantity of the notified chemical = 0.46 X 3.9 = 1.755 tpa

$$PEC = \frac{(1.755 \times 10^9) \text{ mg per annum}}{(230 \text{ days/annum} \times 470 \times 10^6 \text{ L})}$$

$$= 0.016 \text{ mg/L}$$

10:1 dilution on release to outfall = 1.6 µg/L.

These PEC values indicate a significant safety margin when compared to the toxicity results for the notified chemical. The most sensitive species was *Daphnia magna* with a NOEC = 10 mg/L (14 day reproduction test) which gives a safety factor of approximately 5000. The safety factor for the next most sensitive species, green algae, is approximately 30 000 and for fish it is approximately 150 000.

A PEC based on Australia-wide use and the estimated maximum release volume has been calculated:

Maximum Import Volume per annum	100 tonnes
Amount discharged to sewer	13 tonnes
Volume discharged per day	56.5 kg
Sewer output per day*	2700 ML
Concentration in Sewage Treatment Plant	20.7 µg/L
Further diluted (1:10) in receiving waters	2.1 µg/L

*Sewer output based on an Australian population of 18 million, each using 150 L water per day.

The Australia-wide PEC is the same as the Sydney Malabar system release to outfall and gives the same safety factors.

As the coatings containing the notified chemical dry, the chemical will evaporate from the product, enter the atmosphere and be widely dispersed. The chemical should not persist in the atmosphere as it will be quickly broken down in the troposphere.

As the notified chemical will be dispersed at extremely low concentrations over land and water bodies, the use in coatings, cleaning products and chemiluminescent applications should not pose any significant environmental hazard.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Hazard Assessment
In rats, the notified chemical is rapidly absorbed by the gastrointestinal tract, metabolised, and excreted in expired air and in the urine. No tissues preferentially accumulate the notified chemical. One metabolite of the notified chemical, an alkoxy acid, is known to be a developmental toxicant. However, its formation represents a minor route of metabolism.

The notified chemical is of very low acute oral toxicity and low dermal and inhalation toxicity in rats. It is considered slightly irritating to rabbit skin and slightly to moderately irritating to rabbit eye. In guineapigs, the notified chemical was non-sensitising to skin in a non-adjuvant study, but mildly sensitising in an adjuvant study (sensitisation response of 20%).

In repeat dose inhalation or oral studies in rats, the target organs of toxicity were the liver (weight increase, hypertrophy), kidney (weight increase, $\alpha_{2\mu}$-globulin nephropathy in male rats) and adrenals (weight increase, cortical vacuolation). These effects were mostly seen at exposure levels causing sedation. The liver and adrenal effects suggest adaptive responses and were reversible to some extent. The $\alpha_{2\mu}$-globulin nephropathy is a male rat specific effect and not relevant to human risk assessment.

In developmental studies, foetal effects (delayed ossification in rats, increased incidence of supernumerary ribs in rabbits) occurred at exposure levels that caused maternal toxicity. In a two-generation reproduction study in rats, treatment related effects occurred in the liver and kidneys of both parental generations. Treatment related decreased survival and bodyweight occurred in the first filial generation. Reproductive parameters were not affected by treatment in any of the aforementioned studies.

The notified chemical is non genotoxic *in vivo* and *in vitro*.

Based on the results of studies for the toxicological endpoints investigated the notified chemical does not meet the Approved Criteria (NOHSC 1999) for classification of the notified chemical as a hazardous substance.

Occupational Health and Safety
Based on the toxicological profile of the notified chemical adverse human health effects, other than possible immediate eye irritation, are not expected during normal handling and use of the notified chemical. The notifier states that to date there has been no reports of any adverse health effects arising from the use of the notified chemical in other countries.

Considering the molecular weight (<500) and by analogy to other glycol ethers it is assumed that the notified chemical is readily absorbed through the skin. The notified chemical has solvent properties and prolonged or repeated skin contact may result in de-fatting of the skin which may compromise the protective barrier. Subsequent exposure of damaged skin may enhance skin penetration of the notified chemical. Skin contact with the notified chemical during formulation will be limited by use of closed materials transfer systems. The wearing of gloves will also limit exposure during formulation and end use applications. Results from glove permeation studies with the notified chemical show that butyl rubber gloves afford the best skin protection.

Slight to moderate eye irritation is expected if a splash of the notified chemical enters the eye during handling and use of the notified chemical during formulation processes. The probability of a splash incident will be reduced by an enclosed system, adoption of proper work practices and the wearing of eye protection, especially during transfer operations

Most of the toxicological effects attributable to the inhalation of the notified chemical occurred at concentrations approaching a saturated atmosphere (700 ppm) which caused sedation in laboratory animals. Based on a vapour pressure of 0.72 kPa at 20°C, the theoretical saturated vapour concentration of the notified chemical is approximately 710 ppm. In practice this value would not be attained as saturated conditions would not be achieved in the work environment with average natural ventilation. In addition, repeated exposure to sedative concentrations is unlikely because workplaces would have been expected to introduce preventive measures if such exposures had been experienced. Although toxicological effects were observed in experimental animals at non-sedative exposures it is unlikely that toxic inhalation concentrations will be experienced in the workplace. The low volatility of the notified chemical and its proposed manner of use are expected to limit exposure to atmospheric concentrations reaching 100 ppm. Respiratory protection would not be required during normal use and handling under the conditions described. The inhalation risk would be low, considering the vapour pressure of the notified chemical and the expected handling procedures (low probability of spills and an enclosed system).

Public Health

The undiluted notified chemical is not available for direct sale to the public. A small proportion of introduced volumes of the notified chemical in paint strippers and chemiluminescent products, containing the notified chemical at 30% and 70% respectively, will be available to the public. Some members of the public may make dermal and inhalation contact with paint strippers containing the notified chemical, however, these exposures are likely to be relatively brief and intermittent. Exposure to the notified chemical in chemiluminescent products is unlikely under normal circumstances since the notified chemical is contained within a closed system. Although the notified chemical is present at significant concentrations in products available to members of the public, the risk to public health is considered to be low given the low hazard posed by the notified chemical and the brief and intermittent nature of any exposures to products containing the notified chemical. Based on the above information, it is considered that the notified chemical will not pose a significant hazard to public health when used in the proposed manner.

13. RECOMMENDATIONS

To ensure that the described control measures are adequate to minimise inhalation exposure, the notifiers should conduct personal monitoring to determine if worker exposure to the technical grade product during high activity is below the NOAEL of 50 ppm established in the 13-week inhalation study in rats.

Workers should be advised of the potential for occupational dermatoses following repeated skin exposure to the notified chemical and to report any skin changes to their employer or immediate line supervisor at their workplace. When an occupational skin disease occurs, the employer should review work practices and opportunities for contact with the substance and instigate preventive measures to ensure other workers do not develop the same condition. Further guidance on preventing the occurrence of occupational skin diseases can be found in the NOHSC guide *Occupational Diseases of the Skin* (NOHSC 1990).

To minimise occupational exposure to the notified chemical the following guidelines and precautions should be observed:

- Workers should receive regular instruction on good occupational hygiene practices in order to minimise personal contact, and contamination of the work environment with the notified chemical and the formulations that contain it.

- Clothing and gloves are necessary to prevent skin contact - consideration should be given to the ambient environment, physical requirements and other substances present when selecting protective clothing and gloves. Butyl rubber gloves are recommended for commercial grade dialkylene glycol ether. Good work practices dictate that eye protection be worn routinely. Workers should be trained in the proper fit, correct use and maintenance of their protective equipment. Guidance in the selection, personal fit and maintenance of personal protective equipment can be obtained from:

Protective eyewear:	AS 1336 (Standards Australia 1994), Recommended practices for eye protection in the industrial environment; AS/NZS 1337 (Standards Australia/Standards New Zealand 1992), Eye protectors for industrial applications.
Protective clothing:	AS 2929 (Standards Australia 1987) Industrial clothing; or AS 3765.2 (Standards Australia 1990), Clothing for Protection against hazardous chemicals – Limited protection against specific chemicals.
Gloves:	AS 2161.2 (Standards Australia 1998), Occupational

	protective gloves. General requirements.
Occupational footwear:	AS/NZS 2210 (Standards Australia/Standards New Zealand 1994), Occupational footwear.

When dialkylene glycol ether is used in a formulation with other substances the above standards can be used for guidance in the selection of the appropriate protective equipment for a formulated product.

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

The notified chemical is not determined to be a hazardous substance. Products containing the notified chemical may contain hazardous ingredients making the overall product a hazardous substance. Therefore, workplace practices, control procedures and hazard communication products consistent with provisions of State, Territory and Commonwealth legislation based on the *National Model Regulations for the Control of Workplace Hazardous Substance* (NOHSC 1994b) must be in operation.

The notified chemical is classified as a combustible liquid (C1) in accordance with AS 1940 (Standards Australia 1993) and stored and handled in compliance with State, Territorial and Commonwealth regulation for storage and handling of dangerous goods.

14. MATERIAL SAFETY DATA SHEET

The MSDS for the notified chemical was provided in a format consistent with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 1994a).

This MSDS was provided by the applicant as part of the notification statement. It is reproduced here as a matter of public record. The accuracy of this information remains the responsibility of the applicant.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the Act, the director must be informed if any of the circumstances stipulated under subsection 64(2) of the Act arise, and secondary notification of the notified chemical may be required. No other specific conditions are prescribed.

16. REFERENCES

The identity of the notified chemical is claimed as exempt information. In the study titles below the marketing name, “dialkylene glycol ether” replaces the chemical name.

CIVO (1990a): Oral embryotoxicity/teratogenicity study with "dialkylene glycol ether" in New Zealand White rabbits (24 December 1990). Zeist, Netherlands, CIVO. (unpublished study submitted by Dow Chemical (Australia) Limited).

CIVO (1990b): Oral teratology probe study with "dialkylene glycol ether" in New Zealand White rabbits (6 February 1990). Zeist, Netherlands, CIVO. (unpublished study submitted by Dow Chemical (Australia) Limited).

Connell DW (1989): *Bioaccumulation of Xenobiotic Compounds*. Boca Raton: CRC Press.

Environmental Chemistry Research Laboratory (1998): Soil adsorption coefficient determination for "dialkylene glycol ether" (15 January 1998). Midland, USA, The Dow Chemical Company, Environmental Chemistry Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

Environmental Toxicology & Chemistry Research Laboratory (1991a): "dialkylene glycol ether" the toxicity to the green alga *Selenastrum capricornutum* (25 February 1991). Midland, USA, The Dow Chemical Company, Environmental Toxicology & Chemistry Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

Environmental Toxicology & Chemistry Research Laboratory (1991b): The prolonged toxicity of "dialkylene glycol ether" to the rainbow trout (19 February 1991). Midland, USA, The Dow Chemical Company, Environmental Toxicology & Chemistry Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

Environmental Toxicology & Chemistry Research Laboratory (1992): The bioconcentration of "dialkylene glycol ether" in the rainbow trout, *Oncorhynchus mykiss* Walbaum (8 February 1995). Midland, USA, The Dow Chemical Company, Environmental Toxicology & Chemistry Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

Environmental Toxicology & Chemistry Research Laboratory (1998): The uptake and elimination of "dialkylene glycol ether" in the rainbow trout, *Oncorhynchus mykiss* Walbaum (21 January 1998). Midland, USA, The Dow Chemical Company, Environmental Toxicology & Chemistry Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

Health and Environmental Services (1989a): Evaluation of "dialkylene glycol ether" in an *in vitro* chromosomal aberration assay utilising rat lymphocytes (13 November 1989). Freeport, USA, Health and Environmental Services. (unpublished study submitted by Dow Chemical (Australia) Limited).

Health and Environmental Services (1989b): Evaluation of "dialkylene glycol ether" in the Ames salmonella/mammalian-microsome bacterial mutagenicity assay (21 November 1989). Freeport, USA, The Dow Chemical Company, Health and Environmental Services. (unpublished study submitted by Dow Chemical (Australia) Limited).

Health and Environmental Services (1992): Evaluation of "dialkylene glycol ether" in the mouse bone marrow micronucleus test (28 October 1992). Freeport, USA, The Dow Chemical Company, Health and Environmental Services. (unpublished study submitted by Dow Chemical (Australia) Limited).

Howard Pea (1993): Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Vol IV Solvents, pp:280-287. Michigan: Lewis Publishers.

Miller RR et al HELPMMSB (1983): Comparative metabolism and disposition of ethylene glycol monoethyl ether and propylene glycol monomethyl ether in male rats. Toxicol Appl Pharmacol 67:229-237.

NOHSC (1990): Occupational Diseases of the Skin. Canberra: Australian Government Publishing Service.

NOHSC (1994a): National Code of Practice for the Preparation of Material Safety Data Sheets [NOHSC:2011(1994)]. Canberra: Australian Government Publishing Service.

NOHSC (1994b): National Model Regulations for the Control of Workplace Hazardous Substances [NOHSC:1005(1994)]. Canberra: Australian Government Publishing Service.

NOHSC (1999): Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(1999)]. Canberra: Australian Government Publishing Service.

RCC-NOTOX (1989a): 24-hour acute toxicity of "dialkylene glycol ether" to *Daphnia magna* (8 August 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989b): 28 day toxicity study with "dialkylene glycol ether" by daily oral gavage in the rat (26 July 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989c): Acute dermal toxicity study of "dialkylene glycol ether" in the rat (7 March 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989d): Acute eye irritation/corrosion study with "dialkylene glycol ether" in rabbits (8 May 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989e): Assessment of acute oral toxicity with "dialkylene glycol ether" in the rat (17 August 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989f): Assessment of the inherent biodegradability of "dialkylene glycol ether": in the modified Sturm test using pre-adapted inoculum (26 July 1989). s'-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989g): Determination of the boiling point/boiling range of "dialkylene glycol ether" (11 December 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989h): Determination of the density (liquid) of "dialkylene glycol ether" (30 October 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989i): Determination of the fat solubility of "dialkylene glycol ether" (18 December 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX, (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989j): Determination of the freezing point/freezing range of "dialkylene glycol ether" (24 December 1989) 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989k): Determination of the hydrolysis of "dialkylene glycol ether" as a function of pH (31 December 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989l): Determination of the partition coefficient (n-octanol/water) of "dialkylene glycol ether" as a function of pH (20 December 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989m): Determination of the surface tension of an aqueous solution of "dialkylene glycol ether" (14 October 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989n): Determination of the water solubility of "dialkylene glycol ether" (20 December 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1989o): Primary skin irritation/corrosion study with "dialkylene glycol ether" in rabbits (4-hour semi-occlusive application) (9 May 1989). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1990a): 96-hour acute toxicity study in the guppy with "dialkylene glycol ether" (10 July 1990). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1990b): Test for skin sensitization of "dialkylene glycol ether" in the albino guinea pig (Buehler test) (14 March 1990). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1991): Contact hypersensitivity to "dialkylene glycol ether" in the albino guinea pig (Maximization test) (29 November 1991). 's-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1992): *Daphnia magna* reproduction test with "dialkylene glycol ether" (25 March 1992). 's-Hertogenbosch, Netherlands,RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-NOTOX (1993): Terrestrial plant growth test with "dialkylene glycol ether" (5 February 1993). s'-Hertogenbosch, Netherlands, RCC-NOTOX. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-Umweltchemie AG (1991): Acute toxicity (LC50) of "dialkylene glycol ether" to earthworms (9 September 1991). Itingen, Switzerland, RCC-Umweltchemie AG. (unpublished study submitted by Dow Chemical (Australia) Limited).

RCC-Umweltchemie AG (1992): "dialkylene glycol ether": Inherent Biodegradability: Modified Zahn-Wellens Test (11 June 1992). Itingen, Switzerland, RCC-Umweltchemie AG. (unpublished study submitted by Dow Chemical (Australia) Limited).

Standards Australia (1987): AS 2919-1987, Australian Standard Industrial Clothing. Sydney: Standards Australia.

Standards Australia (1990): AS 3765.2-1990, Australian Standard Clothing for Protection against Hazardous Chemicals Part 2 Limited Protection Against Specific Chemicals. Sydney: Standards Australia.

Standards Australia (1993): AS 1940 The Storage and Handling of Flammable and Combustible Liquids. Sydney: Standards Australia.

Standards Australia (1994): AS 1336-1994, Australian Standard Eye protection in the Industrial Environment. Sydney: Standards Australia.

Standards Australia (1998): AS/NZS 2161.2:1998, Australian/New Zealand Standard Occupational Protective Gloves Part 2: General Requirements. Sydney/Wellington: Standards Australia and Standards New Zealand.

Standards Australia/Standards New Zealand (1992): AS/NZS 1337-1992, Australian/New Zealand Standard Eye Protectors for Industrial Applications. Sydney/Wellington: Standards Australia and Standards New Zealand.

Standards Australia/Standards New Zealand (1994): AS/NZS 2210-1994, Australian/New Zealand Standard Occupational Protective Footwear. Sydney/Wellington: Standards Australia and Standards New Zealand.

The Dow Chemical Company (1989): Vapour Pressure of "dialkylene glycol ether" (21 December 1989). Midland, USA, The Dow Chemical Company. (unpublished study submitted by Dow Chemical (Australia) Limited).

The Toxicology Research Laboratory (1990): "dialkylene glycol ether": an acute vapour inhalation study in Fischer 344 rats (28 March 1990). Midland, USA, The Dow Chemical Company, The Toxicology Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

The Toxicology Research Laboratory (1991): "dialkylene glycol ether": a two-week vapour inhalation toxicity study in Fischer 344 rats (6 November 1991), The Dow Chemical Company, The Toxicology Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited). Midland, USA.

The Toxicology Research Laboratory (1992): "dialkylene glycol ether": palatability and 28-day drinking water toxicity study in Sprague-Dawley rats (18 June 1992). Midland, USA, The Dow Chemical Company, The Toxicology Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

The Toxicology Research Laboratory (1993): Pharmacokinetics of "dialkylene glycol ether" in rats (3 March 1993). Midland, USA, The Dow Chemical Company, The Toxicology Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

The Toxicology Research Laboratory (1994a): "dialkylene glycol ether": inhalation teratology study in Fisher 344 rats (14 October 1992). Midland, USA, The Dow Chemical Company, The Toxicology Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

The Toxicology Research Laboratory (1994b): "dialkylene glycol ether": two-generation drinking water reproduction study in Sprague-Dawley rats (15 July 1994). Midland, USA, The Dow Chemical Company, The Toxicology Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

The Toxicology Research Laboratory (1994c): Evaluation of "dialkylene glycol ether" in the Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay (21 January 1994). Midland, USA, The Dow Chemical Company, The Toxicology Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

The Toxicology Research Laboratory (1995): *In vitro* metabolism of propylene glycol ethers (21 January 1998), Midland, USA, The Dow Chemical Company, The Toxicology Research Laboratory. (unpublished study submitted by Dow Chemical (Australia) Limited).

Attachment 1

The Draize Scale (Draize, 1959) for evaluation of skin reactions is as follows:

Erythema Formation	*Rating*	*Oedema Formation*	*Rating*
No erythema	0	No oedema	0
Very slight erythema (barely perceptible)	1	Very slight oedema (barely perceptible)	1
Well-defined erythema	2	Slight oedema (edges of area well-defined by definite raising	2
Moderate to severe erythema	3	Moderate oedema (raised approx. 1 mm)	3
Severe erythema (beet redness)	4	Severe oedema (raised more than 1 mm and extending beyond area of exposure)	4

The Draize scale (Draize *et al*., 1944) for evaluation of eye reactions is as follows:

CORNEA

Opacity	*Rating*	*Area of Cornea involved*	*Rating*
No opacity	0 none	25% or less (not zero)	1
Diffuse area, details of iris clearly visible	1 slight	25% to 50%	2
Easily visible translucent areas, details of iris slightly obscure	2 mild	50% to 75%	3
Opalescent areas, no details of iris visible, size of pupil barely discernible	3 moderate	Greater than 75%	4
Opaque, iris invisible	4 severe		

CONJUNCTIVAE

Redness	*Rating*	*Chemosis*	*Rating*	*Discharge*	*Rating*
Vessels normal	0 none	No swelling	0 none	No discharge	0 none
Vessels definitely injected above normal	1 slight	Any swelling above normal	1 slight	Any amount different from normal	1 slight
More diffuse, deeper crimson red with individual vessels not easily discernible	2 mod.	Obvious swelling with partial eversion of lids	2 mild	Discharge with moistening of lids and adjacent hairs	2 mod.
		Swelling with lids half-closed	3 mod.	Discharge with moistening of lids and hairs and considerable area around eye	3 severe
Diffuse beefy red	3 severe	Swelling with lids half-closed to completely closed	4 severe		

IRIS

Values	*Rating*
Normal	0 none
Folds above normal, congestion, swelling, circumcorneal injection, iris reacts to light	1 slight
No reaction to light, haemorrhage, gross destruction	2 severe

Draize, J. H., Woodward, G., Calvery, H. O. (1944) Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes, J. Pharmacol. Exp. Ther. 82 : 377-390.
Draize J. H. (1959) Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the US, 49 : 2-56.