File No: NA/500

September 1999

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Varisoft 3690

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

VARISOFT 3690

1. APPLICANT

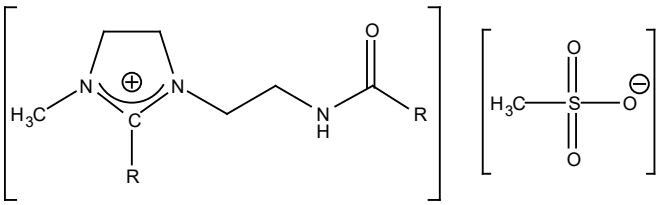
Witco Australia Pty Ltd of 34 MacMahon Street HURSTVILLE NSW 2200 has submitted a standard notification statement in support of their application for an assessment certificate for Varisoft 3690.

2. IDENTITY OF THE CHEMICAL

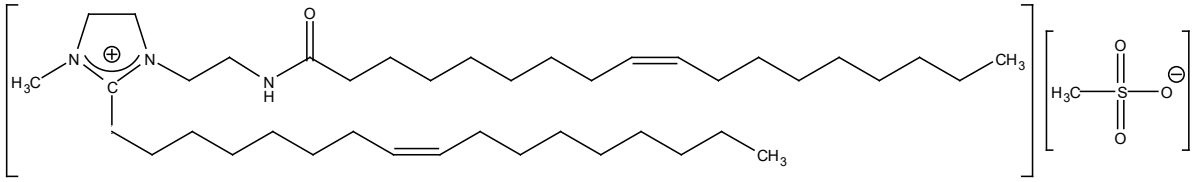
Chemical Name:	1-methyl-2-noroleyl-3-oleic acid-amido ethylimidazolium -methylsulfate
Chemical Abstracts Service (CAS) Registry No.:	72749-55-4
Other Names:	oleic imidazolium methosulfate quaternary ammonium compound
Trade Name:	Varisoft 3690
Molecular Weight:	the molecular weight corresponding to the representative molecular formula is 739; the molecular weight for the constituents is 691 - 743
Molecular Formula:	a representative molecular formula based on the predominant fatty acid (oleic acid) would be: $C_{42}H_{80}O_5N_3S$

Structural Formula:

Generic structure



Main component



Method of Detection and Determination:	^{13}C nuclear magnetic resonance spectroscopy (NMR) was used to establish the identity of the notified chemical
Spectral Data:	^{13}C NMR data were provided

Comments on Chemical Identity

The notified chemical is a UVCB and consists of a mixture of related chemicals. The chemicals have the same generic structure (see above) but differ in the length and degree of unsaturation in the alkyl chains. The alkyl chains are derived from fatty acids and the fatty acid composition of Varisoft 3690 is given. Varisoft 3690 has the same generic structure as Varisoft 475, being manufactured via the same process. However, the fatty acid residues of the two products are derived from different sources - Varisoft 3690 fatty acids are derived from oils and Varisoft 475 fatty acids from tallow. For comparison the fatty acid components of Varisoft 475 are also listed below. Varisoft 475 is used as a fabric softener and in hair care products.

Major fatty acid components of Varisoft 3690

Name	***Molecular formula***	***Weight %***
9-tetradecenoic acid	$C_{14}H_{28}O_2$	3
9-hexadecenoic acid (palmitoleic acid)	$C_{16}H_{32}O_2$	6
9-octadecenoic acid (oleic acid)	$C_{18}H_{34}O_2$	73
9,12-octadecadienoic acid (linoleic acid)	$C_{18}H_{32}O_2$	8
9,12,15-octadecatrienoic acid (linolenic acid)	$C_{18}H_{30}O_2$	1

Major fatty acid components of Varisoft 475

Name	***Molecular formula***	***Weight %***
tetradecanoic acid (myristic acid)	$C_{14}H_{30}O_2$	3
hexadecanoic acid (palmitic acid)	$C_{16}H_{34}O_2$	27
9-hexadecenoic acid (palmitoleic acid)	$C_{16}H_{32}O_2$	5
octadecanoic acid (stearic acid)	$C_{18}H_{36}O_2$	18
9-octadecenoic acid (oleic acid)	$C_{18}H_{34}O_2$	42
9,12-octadecadienoic acid (linoleic acid)	$C_{18}H_{32}O_2$	4
9,12,15-octadecatrienoic acid (linolenic acid)	$C_{18}H_{30}O_2$	1

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	clear to yellow liquid
Boiling Point:	~83°C, that of isopropanol
Flash Point:	15°C
Explosion Limits, **Lower:** **Upper:**	that of isopropanol 2.0% 12.0%
Specific Gravity:	~0.96 at 20°C
Vapour Pressure:	not determined, see comments below
Water Solubility:	~50 mg/L, see comments below
Partition Co-efficient (n-octanol/water):	not determined, see comments below
Hydrolysis as a Function of pH:	not determined, see comments below
Adsorption/Desorption:	not determined, see comments below
Dissociation Constant:	not determined, see comments below

Comments on Physico-Chemical Properties

Given the ionic nature of the notified substance and its high molecular weight it is anticipated that it will have a low vapour pressure.

Originally water solubility was determined by adding 5 g of the notified substance to 5 mL of water. After agitating for one day and centrifugation, a uniform mixture was observed, suggesting a water solubility of >1 000 g/L. This extremely high solubility contrasts sharply with the value of 19.2 mg/L provided for the analogous product Varisoft 475. As noted above, this contains the same quaternary ammonium centre as the notified substance but differs in the size and proportions of the fatty acid derived alkyl substituents. Clarification of this discrepancy was sought from the notifier, who then indicated that the solubility of the notified substance was tested at 50 mg/L and a slight haze developed indicating a dispersion rather than a solution. As a result, the notifier now indicates that the water solubility of the notified substance should be regarded as 50 mg/L.

The notified chemical contains aliphatic hydrocarbon chains coupled to a polar end group. This constitution indicates that the material will have surfactant properties. A possible explanation for the discrepancy between the two water solubility measurements for the notified substance may lie in the formation of micelles by this surface active substance. In the original study the concentration of the substance exceeded its critical micelle concentration (CMC). As a result, micelles or other tertiary structures resulted, solubilising the substance and a uniform solution was observed. In the latter test, the concentration of the substance was below the CMC and hence it was unable to form micelles. Precipitation of the substance was observed as the concentration of the substance exceeded the "true solubility" of the substance. This explanation would be consistent with the observed value of 19.2 mg/L being a "true solubility"observed for Varisoft 475. However, without details of the test for Varisoft 475 and the CMCs for both substances, this hypothesis cannot be verified.

The notifier has submitted a study on the hydrolytic behaviour of the notified substance at varying temperature and pH according to OECD Test Guideline 111 (Organisation for Economic Co-operation and Development 1995-1996). Only the pH of the buffered solutions was reported in the experiments. The pH of the solutions remained unchanged in the solutions buffered at pH 4, 7 and 9 and slight variations were observed in the solution buffered at pH 1.2. The buffering capacity in the solutions would be expected to absorb any change in the pH resulting from hydrolysis. Hence, it is difficult to conclude anything about the hydrolytic behaviour of the notified substance in these systems without data on the variation of the concentration of the substance in these systems with time. Thus, it is unclear whether the notified substance is likely to undergo hydrolytic decomposition of the amides in the environmental pH range of 4-7, which is theoretically possible due to its solubility.

Assuming that the water solubility is 50 mg/L the substance is expected to have a moderate octanol/water partition coefficient (log Pow) but this may be enhanced by its surface activity.

Based on the anticipated surface activity the substance would be expected to strongly adsorb to sediments. Quaternary ammonium compounds are known to react with dissolved organic carbon in water to form part of the sediments, and become completely inactivated on contact with soils (Nabholz JV Miller P Zeeman M 1993). They have also been shown to adsorb on a wide variety of materials (Boethling RS Lynch DG 1992). The data provided for Varisoft 475 indicates in separate experiments that, after 1 hour incubation, 32% adsorbed to influent

sewage, 90% to activated sludge, 64% to river water and 76% to river water with sediment (Dynamic Corporation 1987). No experimental details were provided. For quaternary ammonium polymers with a number average molecular weight between 500 and 1 000. The US EPA assumes typical removal rates of between 50-90% (Boethling RS Nabholz JV 1997).

The notified substance contains no dissociable hydrogen atoms or basic functionalities.

4. PURITY OF THE CHEMICAL

Degree of Purity: 70-80%

Toxic or Hazardous Impurities: none known

Impurities (> 1% by weight):

Chemical class:	imidazoline amine
Weight percentage:	12-18%
Chemical class:	quaternised ring open amine
Weight percentage:	8-12%

Additives/Adjuvants: isopropanol ~ 24%

5. USE, VOLUME AND FORMULATION

The notified chemical is to be used as an additive in toilet and facial tissue manufacture. It will be used exclusively at one site in Australia. Claims were made and accepted for the detailed end use of the notified chemical to be exempt from publication in this Full Public Report.

Varisoft 3690 containing the notified chemical will not be manufactured in Australia but will be imported in 1 000 L poly-Schutz tanks. Varisoft 3690 contains approximately 24% of the solvent isopropanol and ~76% of the notified chemical. Import volumes for the product Varisoft 3690, are expected to be about 30 tonnes per annum in the first five years. This corresponds to 24 tonnes of the notified chemical per annum.

The notified chemical (60 tonnes) was introduced for use in Australia under a Section 30 Permit obtained in March 1997.

6. OCCUPATIONAL EXPOSURE

Varisoft 3690 will be transported in 1 000 L Schutz conatiners to the notifier's site. Waterside and transport workers will not be exposed to Varisoft 3690 except in the event of a spill.

The Varisoft 3690 containers will be received at the mill's chemical store by store workers (4 personnel, 5 minutes per week). Similarly, storepersons are unlikely to be exposed to the notified chemical unless a spill occurs.

The addition of Varisoft 3690 to cellulose fibres occurs three shifts per day with 5 workers per shift in attendance. Workers potentially exposed include, hydrapulper, machine, drying and winder operators, and maintenance workers. The activities performed by these personnel are as follows.

A hydrapulper operator (30 minutes per week) transports the product by forklift to the paper machine area, where it is transferred to an open top storage tank of the machine. Dermal and ocular exposure to the concentrated form of the notified chemical may occur as lines are connected/disconnected from the import container to the storage tank. The notifier states that the hydrapulper operator is required to wear eye protection and gloves during this activity.

The product is automatically diluted with water by an in-line mixer to a concentration of 4% or less. The diluted product flows into a tank, along with the suspension of fibres and additives. The concentration of free notified chemical at this stage is approximately 12 ppm, as the notified chemical is largely bound to the fibres. Due to the automated nature of this process, worker exposure is unlikely, unless splashing occurs.

Good ventilation is provided in the process area.

The machine operator, and occasionally the dryer operator are responsible for manually adjusting a dosing pump or changing a set-point on the control system to ensure the correct rate of delivery of the product containing the notified chemical and additives to the batch. Dermal exposure may occur as the operator fills a measuring cylinder to check the flow rate. This activity takes about 80 minutes per week.

Winder operators may receive dermal exposure to the notified chemical from contact with the manufactured paper tissue which contains approximately 0.2% of the notified chemical. However, the notifier has stated that the notified chemical is bound to the fibre matrix by this stage of the process.

Maintenance workers may be potentially exposed to the notified chemical if repairs to the system are required. The notifier estimates that up to five workers may come into contact with the notified chemical, for a period of two minutes per week. The notifier states that plant maintenance work is conducted only after the relevant section has been isolated in accordance with a documented procedure.

The notifier states that there is a site-wide requirement to wear safety glasses. Additional personal protective equipment, in the form of gloves, aprons, respirators, goggles, wet weather protective clothing, face shields and protective footwear, is used when required.

Occupational exposure to the final products containing the notified chemical will occur, for example laboratory and health care personnel, however, as stated above the notified chemical is bound to the fibre matrix.

7. PUBLIC EXPOSURE

The final concentration in tissue products of Varisoft 3690 is approximately 0.2% w/w and the compound is strongly bonded to the tissue fibres. Because of the intended use of the notified chemical, direct and wide spread public exposure to the compound is unavoidable. The route of exposure will be almost entirely dermal, to limited areas of the body and of short duration, probably measurable in seconds in most cases. In certain human health conditions, however, individual exposure will be repetitive over some days.

In the event of a transport accident a significant volume of the notified chemical may be released, however, as the major hazard would come from direct contact with the material, the risk to the public would be low. Spilt material is recovered using absorbent material, with disposal to land fill or incineration, in accordance with local government regulations.

During the manufacture process Varisoft 3690 is added to the paper pulp as a liquid via an automatic mixer. The potential for public exposure through this process is slight.

8. ENVIRONMENTAL EXPOSURE

Release

Paper manufacture

The notifier has indicated that the notified substance will be used in the manufacture of facial tissue (1 160 tonnes per month) and toilet tissue (2 040 tonnes per month) at a single pulp and paper mill. The total use of the notified substance per month will be around 2 tonnes. The substance will be added to a slurry of cellulose fibres in water which will be collected on moving screens and dried to form the tissues. Waste water containing up to 3% of the cellulose fibres and remaining notified substance will then be fed into the mill's on site waste water treatment plant. The notifier claims that greater than 99% of the notified substance will adsorb to the paper fibres and have provided testing on the wastewater samples from paper making to support the high rate of adsorption.

The waste water passes through a clarifier and a series of aerobic treatment ponds. The average residence time in the ponds is around 10 days and the flow rate through the ponds is 50 ML/day. Solids from the clarifier are sent off-site and used in a compost making process which takes 12 weeks.

Facial Tissue

The majority of the substance bound to facial tissue is expected to end up in landfill after disposal in domestic waste. Hence it may be anticipated that the majority of the notified

substance used in facial tissues (625 kg per month assuming 99% adsorption to tissue during manufacture) will be disposed of to landfill.

Toilet tissue

The majority of the notified substance bound to toilet tissue is expected to be released to the municipal sewage system. The notifier estimates that a small percentage (~5%) may end up in septic tanks. If all the notified substance bound to toilet tissue ends up in sewer this would correspond to 1.1 tonnes per month assuming 99% adsorption to tissue during manufacture.

Fate

The notified substance is not readily biodegradable (calculated as the ratio of the amount of CO_2 produced to the theoretical carbon dioxide ($ThCO_2$), and expressed as a per cent). Biodegradation amounted to 7.2% at the end of the 28-day exposure to activated sludge from a domestic sewage treatment facility in the CO_2 Evolution (Modified Sturm) Test for ready biodegradability (Organisation for Economic Co-operation and Development 1981). The notified substances inherent biodegradability was not measured but based on this result it would not be expected to be highly persistent.

The notifier has also supplied data on the biodegradation of the analogous substance Varisoft 475. Measurements of the biological oxygen demand (BOD) increased steadily over the 30 days of the study with the ratio of the BOD to the chemical oxygen demand (COD) as shown below:

Day	5	10	20	30
BOD/COD	0.02	0.12	0.15	0.19

Provided Varisoft 475 was the only carbon source for the activated sludge, these data provide support that the notified substance is biodegradable but would not meet the ready biodegradable criteria under the conditions used in the experiment, that is, $BOD_5/COD > 0.5$. The relatively high molecular weight and charged nature of the notified chemical indicate that it is unlikely to bioaccumulate (Connell DW 1989). It is noted that, for the analogue Varisoft 475, a bioconcentration factor of 10.7 is said to have been measured for bluegill sunfish, exposed to 8.8 g/L of the substance in a flow through system (Dynamic Corporation 1987), again no further details were provided).

Waste water from the tissue making process will be discharged through the paper mills on-site treatment plant. This waste will contain a maximum of 66 kg of the notified substance per month based on 99% adsorption during paper making, of which between 50 kg will be associated with waste paper fibres (notifier estimates that ~3 t of fibre may be lost each day from tissue paper machines using the notified substance). In the treatment plant the water passes through a clarifier to remove suspended solids then passes through three serial aeration ponds. Suspended solids removed by the clarifier are used in a composting process. Substance bound to the suspended solids (less than 50 kg per month bound to waste fibres) is expected to degrade during the 12 week composting process. Based on data for the analogue, and the US EPA assumptions (Boethling RS Nabholz JV 1997) for cationic polymers with molecular weights between 500 and 1 000, it is anticipated that between 50 and 90% of the notified substance may be removed, either by adsorption or degradation, during the passage

of the waste water through the treatment plant before the effluent is discharged into receiving waters via the 11 km drainage channel from the plant.

Notified chemical which is bound to the tissues is expected to remain so and share their fate. Notified chemical adsorbed to toilet tissue is therefore expected to form part of the sewage sludge, which will be incinerated or landfilled. Incineration of the notified substance will result in its destruction to form water and oxides carbon and nitrogen. Waste chemical consigned to landfill, either adsorbed to facial tissues or as part of the sewage sludge, is expected to degrade over time as a result of the biological activity in landfill.

9. EVALUATION OF TOXICOLOGICAL DATA

Varisoft 3690, containing the notified chemical (~70-80%) is a UVCB (chemical of unknown or variable composition or of biological origin) and differs from similar existing chemicals Varisoft 445 and Varisoft 475 on the basis of the source of the fatty acid component. The source of the fatty acid for Varisoft 3690 is vegetable oil and for Varisoft 445 and Varisoft 475, soft tallow. Varisoft 475 has an alkyl distribution of C_{14-18} and C_{16-18} unsaturated, Varisoft 445 has an alkyl distribution of C_{14-18}. For a number of schedule requirements, the notifier has submitted the results of studies conducted on structurally similar analogues, including Varisoft 475. The notifier claims that the toxicity of the analogues would be very similar to that of the notified chemical.

Complete test reports were available for a number of the studies. For other studies, only a summary of results was provided.

In the toxicological summaries below, the chemical used in the study is indicated.

9.1 Pharmacokinetics (FSQSC 1988)

Analogue: A summary of a study conducted with Varisoft 445 was provided.

The absorption, distribution and excretion of the analogue Varisoft 445, via oral administration and dermal application was investigated in rats. As with Varisoft 475, Varisoft 445 differs from the notified chemical with respect to its source of fatty acid (hydrogenated tallow) and distribution of alkyl groups. The investigations were conducted using radiolabelled Varisoft 445: the N-methyl group of Varisoft 445 was labelled with ^{14}C.

Following oral administration, the bulk of the dose was excreted within 24 hours (87.53% as faeces, urine and CO_2, with the amount in faeces accounting for 87.00%). At 72 hours, 5.09% of the dose was still present in various tissues. A half-life of approximately 12 hours was calculated. Very little of the administered dose appeared in exhaled CO_2 indicating that the labelled site is not metabolically active, probably because the quaternary ammonium center is sterically hindered. As most of the dose was excreted through the faeces an investigation to assess uptake across the gut wall was conducted by measuring the administered dose in bile. In this study similar kinetics were observed, at 72 hours faecal excretion accounted for 93.1% of the administered dose, with 0.074% of the dose in bile. The dose still present in various tissues at 72 hours was 0.338%. The half-life calculated in this uptake study was approximately 9.4 hours.

The findings from dermal application revealed that at 72 hours, 89% of the applied radiolabelled dose was still present at the site of application, with the remainder distributed as follows: adjacent to application site (0.0002%); body, all tissues (including bone marrow) and fluids (0.30%); and excreted in faeces (0.03%) or urine (0.03%). The fraction of label absorbed was determined to be 0.4%. However, it was considered that this amount may in the main be due to the presence of an impurity, with the true amount of test substance absorbed being 0.0095%. Clearance of the absorbed dose from the blood is rapid and occurs via the renal and the entero-hepatic circulation.

These results indicate that the test substance is very poorly absorbed from the gastrointestinal tract or dermally and what little is absorbed is rapidly excreted. From these investigations it would appear that imidazolium quaternary ammonium compounds will not accumulate in the body to any significant extent as a result of repeated ingestion or dermal contact.

9.2 Human Exposure Potential (FSQSC 1988)

The estimated absorbed dose per day from wearing of clothing treated with an imidazolium quaternary ammonium compound has been calculated as less than 0.0035 μg/kg day for a 70 kg person.

The calculation assumes 90% of the skin surface (skin surface of a 70 kg person is 22 000 cm^2) is in contact with fabric containing a quaternary ammonium level of 01.3 $\mu g/cm^2$ and an absorbed dermal dose of 0.0095% per unit of body weight, which is taken from the pharmacokinetic study above.

9.3 Summary of Acute Toxicity of Varisoft 3690

Test	***Species***	*Outcome*	***Reference***
acute oral toxicity:	rat		
5% solids		LD_{50} > 20 000 mg/kg	(Harris DL 1975)
76% solids		LD_{50} > 20 000 mg/kg	(Harris DL 1975)
acute dermal toxicity		test not conducted	
acute inhalation toxicity		test not conducted	
skin irritation:	rabbit		
5% solids		slight irritant	(Harris DL 1975)
76% solids		moderate irritant	(Harris DL 1975)
90% solids		severe irritant	(Thompson GW 1981)
eye irritation:	rabbit	moderate irritant	(Thompson GW 1981)
		corrosive	(Harris DL 1975)
5% solids		corrosive	(Thompson GW 1981)
76% solids			
90% solids			

Summary of Acute Toxicity of Varisoft 475

Test	*Species*	*Outcome*	*Reference*
acute dermal toxicity	**rabbit**	**LD50 > 1.8 g/kg**	
skin irritation up to 5% w/v	**human**	**non-irritating**	(FSQSC 1988)
skin sensitisation:	guinea pig		
Buehler, 1% w/v			
Lot 1138-K:		non-sensitising	(Thompson GW 1981)
Lot 195-136:		non-sensitising	(Thompson GW 1981)
Lot 1104-K:		sensitising	(FSQSC 1988)
			(FSQSC 1988)
Buehler, 5% w/v		sensitising	
skin sensitisation: repeat insult, 0.25% w/v	human	not sensitising	(FSQSC 1988)

9.3.1 Oral Toxicity

Test 1 was conducted by **(**Harris DL 1975) and Test 2 by (Harris DL 1975).

Test Substance	Test 1: Varisoft 3690 5% solids Test 2: Varisoft 3690 76% solids
Species/strain:	rat/Sprague-Dawley
Number/sex of animals:	6 males/dose/test
Observation period:	14 days
Method of administration:	Test 1: 5, 10, and 20 g/kg administered by gavage Test 2: 5, 10, and 20 g/kg administered by gavage
Clinical observations:	not stated
Mortality:	Test 1: none; Test 2: one rat died three days after administration of the 20 g/kg dose
Morphological findings:	not stated
Test method:	similar to OECD guidelines

LD_{50}:	Test 1: > 20 g/kg; Test 2: > 20 g/kg
Result:	the notified chemical (at 5% or 76% solids) is of very low acute oral toxicity

9.3.2 Dermal Toxicity

Notified Chemical: test not conducted.

Analogue: A summary of a study conducted with Varisoft 475 was provided.

Varisoft 475 at 2 mL per kg (1.8g active/kg) was applied for 24 hours to rabbit skin. The minimum lethal dose was greater than 1.8 grams active compound per kg. (FSQSC 1988).

9.3.3 Inhalation Toxicity

Notified Chemical: test not conducted.

9.3.4. Skin Irritation

9.3.4.1 **Skin Irritation in Humans** (FSQSC 1988)

Analogue: A summary of a study conducted with Varisoft 475 was provided.

Varisoft 475 was tested in three 24 hour exposures over a 6 day period at concentrations of 0.5, 1.0 and 5% w/v, in a dose volume of 0.3 mL via an occluded patch. No skin irritation was observed.

9.3.4.2 Skin Irritation in Rabbits

Tests 1, 2 and 3 were conducted by **(**Harris DL 1975), (Harris DL 1975), (Thompson GW 1981), respectively.

Test Substance	Test 1: Varisoft 3690, 5% solids Test 2: Varisoft 3690, 76% solids Test 3: Varisoft 3690, 90% solids
Species/strain:	rabbit/New Zealand white
Number/sex of animals:	3/sex/test
Method of administration:	Test 1 and 2: test substance applied to two sites per animal, an abraded and non-abraded site, and held under occlusive dressing for four hours; Test 3: 0.5 mL of the test substance was applied to the shaved back of each animal and held under occlusive dressing; after 4 hours the test site was washed with water;

Observation times after application:	Test 1: 2, 4, 24, 48 and 72 hours Test 2: 2, 4, 24, 48 and 72 hours Test 3: 4, 24 and 48 hours

Draize scores[a] of non-abraded skin

Test 1 Varisoft 3690, 5 % solids

	Time after treatment (hours)				
Animal #	***2***	***4***	***24***	***48***	***72***
Erythema					
1	0	1	1	1	0
2	0	1	1	1	1
3	0	1	1	1	0
4	0	1	1	1	1
5	0	1	1	1	0
6	0	1	1	1	0
Oedema					
1	0	0	0	0	0
2	0	0	1	1	0
3	0	0	0	0	0
4	0	0	1	1	0
5	0	0	0	0	0
6	0	0	0	0	0

[a] see Attachment 1 for Draize scales.

Draize scores[a] of non-abraded skin (continued)

Test 2 Varisoft 3690, 76 % solids

	Time after treatment (hours)				
Animal #	***2***	***4***	***24***	***48***	***72***
Erythema					
1	0	1	2	2	2
2	0	1	2	2	2
3	0	1	2	2	2
4	0	1	2	2	2
5	0	1	2	2	2
6	0	1	2	2	2
Oedema					
1	0	0	1	1	1
2	0	0	1	1	1
3	0	0	1	1	1
4	0	0	1	1	1
5	0	0	1	1	1
6	0	0	1	1	1

[a] see Attachment 1 for Draize scales

Draize scores[a] of non-abraded skin (continued)

Test 3 Varisoft 3690, 90 % solids

	Time after treatment (hours)				
Animal #	***2***	***4***	***24***	***48***	***72***
Erythema					
1		1	2 [B]	3 [B]	-
2		1	3 [B]	3 [B]	-
3		1	3 [B]	3 [B]	-
4		1	3 [B]	3 [B]	-
5		1.5	3.5 [B A]	3.5 [B A]	-
6		1.5	2.5[B]	2.5 [B]	-
Oedema					
1		1	3	3	-
2		1	4	3	-
3		1	4	3	-
4		1	4	3	-
5		1	3	3	
6		1	2.5	2.5	-

[a] see Attachment 1 for Draize scales
[B] Blanching. [A] Subcutaneous haemorrhage.

Test method:	Test 1 and 2: in accordance with US Dept of Transport (DOT) skin test; Test 3: in accordance with Title 49, Code of Federal Regulation, 173.1200, Appendix A (USA);
Observations:	Test 3: areas of blanching were observed in all animals at the 24 and 48 hour observation period; areas of subcutaneous haemorrhage were seen in one animal at 24 and 48 hours; corrosivity was not observed at the 24 and 48 hour observation time
Comment:	for Test 2 and Test 3, the observation times did not extend beyond 72 and 48 hours, respectively, even though dermal responses were still present at these times, therefore, the reversibility of the dermal effects cannot be evaluated
Result:	Test 1: at 5%, the notified chemical was a slight irritant to rabbit skin; Test 2: at 76%, the notified chemical was slight to moderate irritant to rabbit skin; Test 3: at 90%, the notified chemical was a moderate to severe irritant to rabbit skin;

9.3.5 Eye Irritation

Tests 1, 2 and 3 were conducted by **(**Thompson GW 1981), (Harris DL 1975), and (Thompson GW 1981), respectively.

Test Substance	Test 1: Varisoft 3690, 5 % solids Test 2: Varisoft 3690, 76 % solids Test 3: Varisoft 3690, 90 % solids
Species/strain:	rabbit/New Zealand White
Number/sex of animals:	3/sex/test
Observation period:	7 days
Method of administration:	0.1 mL of the test substance placed on the everted lower lid of one eye; the contralateral eye served as the control
Observation times after application:	Test 1: 24, 48, 72 and 96 hours and 7 days Test 2: 24, 48 and 72 hours Test 3: 24, 48, 72 and 96 hours and 7 days

Draize scores[a] of non-irrigated eyes:

Test 1: VARISOFT 3690, 5% solids

	Time after Instillation									
Animal	***1 day***		***2 days***		***3 days***		***4 days***		***7 days***	
Cornea	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0
Iris										
1	0		0		0		0		0	
2	0		0		0		0		0	
3	0		0		0		0		0	
4	0		0		0		0		0	
5	0		0		0		0		0	
6	0		0		0		0		0	

Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	2	1	0	1	0	1	1	0	0	0.5	0	0	1	0	0
2	2	1	1	0	1	0	0	0	0	1	0	0.5	0	0	0
3	2	1	1	1	1	0	0.5	0	0	0	0	0	0	0	0
4	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0
5	1.5	1	0	1	1	0	0.5	0	0	0	0	0	0	0	0
6	2	1.5	1	1.5	1	0	1	0	0	0	0	0	0	0	0

[1] see Attachment 1 for Draize scales

o opacity, a area, r redness, c chemosis, d discharge

Draize scores[a] of non-irrigated eyes (continued):

Test 2: VARISOFT 3690, 76% solids

	Time after Instillation					
Animal	***1 day***		***2 days***		***3 days***	
Cornea	***o***	***a***	***o***	***a***	***o***	***a***
1	0	0	0	0	No readings given	
2	0	0	0	0		
3	0	0	0	0		
4	0	0	0	0		
5	0	0	0	0		
6	0	0	0	0		
Iris						
1	0	0	0	0	No readings given	
2	0	0	0	0		
3	0	0	0	0		
4	0	0	0	0		
5	0	0	0	0		
6	0	0	0	0		

Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	3	3	3	3	3	3	Scores not given, but reported as corrosive, irreversible damage to the eye		
2	2	2	2	2	2	2			
3	3	2	2	3	2	2			
4	3	2	2	3	2	2			
5	3	2	2	3	2	2			
6	3	3	2	3	3	2			

[1] see Attachment 1 for Draize scales

o opacity, a area, r redness, c chemosis, d discharge

Draize scores[a] of non-irrigated eyes (continued):

Test 3: VARISOFT 3690, 90% solids

	Time after Instillation									
Animal	***1 day***		***2 days***		***3 days***		***4 days***		***7 days***	
Cornea	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***
1	1.5	4	2	4	3	1.5	4	2	2.5	2
2	E 100 4	1	E 100 4	1	E 75 4	1	E 75 4	1	E 50 3	4
3	E 100 4	1	E 100 4	1	E 100 3	2	E 100 3	3	E 100 3	2
4	E 100 1.5	3	E 100 2	2	E 60 2.5	2	E 100 L 2	1.5	E 10 2	1
5	E 100 4	1.5	E 60 4	2	E 40 3	4	E 30 4	1.5	E 10 4	4
6	E 100 2	4	E 100 4	1.5	E 100 3	4	E 100 4	2	E 100 4	2
	E 100		E 100		E 100		E 100 L		E 80	
Iris										
1	1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}	
2	1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}	
3	1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}	
4	1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}	
5	1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}		2^{U}	
6	1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}		1^{INJ}	

Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	2	4	3	2.5	4	3	3	3	3	3	3	3	2	2.5	2
2	2	4	3	2.5	4	3	3	4	3	3	3.5	3	3	3	2
3	2	4	3	2	4	3	3	3.5	3	3	3	2.5	2.5	3	2
4	2.5	3	3	2.5	3	3	2.5	1	1	2.5	2	0	2	1.5	0
5	2.5	4	3	2.5	4	3	3	4	3	3	3.5	3	2.5	2.5	3
6	2.5	4	3	2.5	4	3	3	3.5	3	3	3.5	3	2	2	0

Sodium Fluorescein Examination					
1	-	-	Pos 75%	-	Pos 50%
2	-	-	Pos 100%	-	Pos 100%
3	-	-	Pos 60%	-	Pos 10%
4	-	-	Pos 40%	-	Pos 10%
5	-	-	Pos 100%	-	Pos 100%
6	-	-	Pos 100%	-	Pos 86%

[1] see Attachment 1 for Draize scales. o opacity, a area, r redness, c chemosis, d discharge
INJ = injected. U = unable to visualise due to opacity. E = corneal epithelium damage, peeling, %.
L = corneal oedema

Test method:	similar to OECD test guidelines
Comment:	Test 1: no lesions of the iris or cornea were observed; conjunctival lesions were resolved by Day 7 in all but one animal; purulent and/or clear discharge was observed at 24 and 48 hours; the sodium fluorescein examination[1] was negative at 72 hours; Test 2: no lesions of the iris or cornea were observed at the 24 and 48 hour observation times; no readings provided for cornea, iris or conjunctiva, at 72 hours other than the statement 'corrosive'; Test 3: blanching of the conjunctivae was exhibited by all animals at the 24, 48, 72 and 96 hour observations; the conjunctivae appeared necrotic in all animals at 48, 72 and 96 hours; areas of petite haemorrhage were observed in the conjunctivae of one animal at 48 hours; hypopyon[2] was exhibited in one animal at 72 hours and in two animals at 96 hours; pannus[3] was seen in two animals at 96 hours and in five animals at 7 days, sodium fluorescein examinations were positive at 72 hours and 7 days;
Result:	at 5% the notified chemical was mildly irritating to the eyes of rabbits, producing slight conjunctival effects; at 76% the notified chemical was reported as corrosive to the eyes of rabbits; at 90% the notified chemical was a severe eye irritant

9.3.6 Skin Sensitisation Studies

9.3.6.1 Buehler Method (Thompson GW 1981), (Thompson GW 1981), (FSQSC 1988)

For this skin sensitisation investigation, the study was conducted using three lots of Varisoft 475. Full studies were provided in the notification dossier for the Lot 1138K (Thompson GW 1981) and Lot 195-136 (Thompson GW 1981). A summary only was available for the results of testing done on Lot 1104-K (FSQSC 1988).

[1] Used to detect epithelial lesions of the cornea and conjunctiva.
[2] An accumulation of pus in the anterior chamber of the eye.
[3] Vascularisation and connective tissue deposition beneath the epithelium of the cornea.

Test Substance (analogue):	Lot 1138-K: Varisoft 475 (75%) Lot 195-136: Varisoft 475 (85%) Lot 1104-K: Varisoft 475 (75%)
Species/strain:	guinea pig
Number of animals:	Lot 1138-K: 20 test, 4 naive control; Lot 195-136: 20 test, 4 naive control; Lot 1104-K: 20 test
Induction procedure:	Lots 1138-K, 195-136 and 1104-K: 0.4 mL of a 1% (w/v) solution of the test substance in 0.8% saline was applied, via a patch, to the shaved midline of the back of each animal and held under occlusive dressing for 6 hours; this was repeated each week for another 2 weeks; induction concentrations of the test substance were limited to 1% due to irritation known to occur at 5%
Challenge procedure:	Lot 1138-K and 195-136: 2 weeks following the administration of the third induction dose, each test animal was challenged with 1% of the test substance applied to a newly clipped site; the naive control animals were also treated with the challenge application in the same manner; 24 hours after primary challenge, the test area was depilated with Neet cream hair remover (30 min. application, then washed away with warm water); treatment sites were read and scored 26 and 48 hours after primary challenge; Lot 1104-K: no details available
Challenge outcome:	Lot 1138-K: test animal: one male and three females reacted to the challenge application with a very faint nonconfluent erythema at the 24 hour observation period; naive controls: one male reacted with a very faint nonconfluent erythema; because the skin reaction in the treated animals did not exceed the most severe control reaction, the responses were not substantial enough to be considered positive for sensitisation; Lot 195-136: one male and one female reacted to the challenge application with a very faint nonconfluent erythema at the 24 hour observation period; both of the responses were not considered positive for sensitisation; Lot 1104-K: details not available other than one animal showed evidence of sensitisation

Test method:	conformance to established regulatory test guidelines not indicated
Result:	Varisoft 475 under the conditions of this study was sensitising to the skin of guinea pigs using an induction and challenge concentration of 1% w/v

9.3.6.2 Buehler Method (FSQSC 1988)

This study was conducted on Varisoft 475 (90%). Only a summary of the test results was submitted by the notifier.

Guinea pigs received an induction concentration of 25% for six hours per week for three weeks. Two weeks after induction a 5% challenge concentration was applied for a single 6-hour occluded exposure. Seventeen out of 20 animals showed evidence of sensitisation.

9.3.6.3 Human Repeat Insult Patch Test (FSQSC 1988)

The study was conducted on Varisoft 475 (90%). Only a summary of the test results was submitted by the notifier.

Volunteers (n = 217) received 9 exposures to an induction concentration of 0.25% aqueous Varisoft 475 (0.3 mL/occluded patch) applied for a 24 hour period, three times a week during a three week induction period. Two weeks later a challenge dose of 0.25% aqueous was applied in a single 24-hour occluded patch. It is reported that none of the volunteers were sensitised to Varisoft 475 (90%).

9.4 Repeat Dose Toxicity

Notified Chemical: tests not conducted.

9.4.1 Two week oral study in dogs (Goldenthal EI 1993)

The aim of this study was to determine the palatability of Varisoft 475 (75%) when administered in the diet of dogs. Results of the study were used to determine doses for a subsequent 8-week toxicity study in dogs. The 8-week study was not provided by the notifier and it is not apparent whether the study has actually been conducted.

Test Substance(analogue)/ Purity:	Varisoft 475 (75%); 76.6%
Species/strain:	dog/beagle
Number/sex of animals:	1/sex/dose
Method of Administration:	*ad libitum*
Dose/Study duration:	nominal dietary concentrations of the test substance at 0, 1 000, 3 000, 10 000 and 30 000 ppm active ingredient

	for 2 weeks; average test substance consumption: males - 37.3, 103.0, 256.2 and 817.9 mg/kg/bwt/day, females - 40, 92.0, 270.2 and 798.1 mg/kg/bwt/day
Mortality:	none
Clinical observations:	overt toxicity was recorded on Day 10 for the female dog at 3 000 ppm; soft stool and/or diarrhoea in the higher dose groups for both males and females; soft stool was also recorded in the control female; red material was observed in the stool of males at 3 000 and 10 000 ppm; food consumption was decreased in the first week of the study for all test animals, which persisted into week 2 for females of the 10 000 and 30 000 ppm group; all dogs lost weight during the first week of study;
Clinical Chemistry/Haematology	no haematology or clinical chemistry was performed
Histopathology:	no histopathology was performed
Test method:	conformance to established regulatory test guidelines not indicated
Result:	in the absence of serum chemistry and haematological tests and histopathological examination a No Observed Effect Level (NOEL) cannot be established

9.4.2 Repeat Oral Dose Studies in Rats (FSQSC 1988)

Analogue: The following data for Varisoft 475 were provided in summary form.

Rats, 20/sex/dose, were adminstered Varisoft 475 at doses of 0, 10, 100 or 1 000 mg active ingredient for 13 weeks (91 days). No treatment related changes in body weight or food consumption were observed. High dose males showed lower absolute and relative liver weights and changes in serum chemistry consisting of lower total protein and higher serum glutamic pyruvic transaminase values. The study authors indicate this effect was not accompanied by histopathologic evidence of hepatic injury and appears to be most likely due to impaired nutrient uptake in test animals. Histopathologic examination of the bone marrow revealed no treatment related changes. The reported NOEL was 100 mg/kg/bwt/day.

A 28 day repeat dose study has also been conducted however, other than reporting a NOEL, no other details of the study have been submitted (FSQSC 1988). The NOELs from the 28 day and 91 day oral repeat dose studies are summarised below:

Exposure Duration	*Dose*	*NOEL/effects summary*
28 days	4 mg/kg bwt 40 mg/kg bwt 400 mg/kg bwt	400 mg/kg bwt/day; minor changes in serum enzymes (male/female) and in bilirubin (female) at 400 mg/kg bwt
91 days	10 mg/kg bwt 100 mg/kg bwt 1 000 mg/kg bwt	100 mg/kg/bwt/day; reduced liver weight and minor serum enzymes changes in males at 1 000 mg/kg bwt

9.4.3 Repeat Dose Dermal Studies in Rabbits (TSCATS 1988)

Analogue: The following data for Varisoft 475 were provided in summary form.

In a repeat dose dermal study, rabbits, 5/sex, received topical application of 2 mL per kg bwt per day of Varisoft 475 at dose levels of 3 or 27 mg active compound per kg bwt per day for 13 weeks (91 days). Animals at both doses had slight to moderate erythema, oedema and desquamation. There were no treatment related changes in body weight. No treatment related changes were observed in clinical pathology, bone marrow smears, organ weights, microscopic changes in skin or histopathological changes to internal organs. The reported NOEL for systemic toxicity was 27 mg active compound per kg bwt per day.

In other repeat dose studies of 14 day or 91 day duration (no other details provided), no effects other than skin irritation were reported for Varisoft 475 (FSQSC 1988). The NOELs from the studies on Varisoft 475 are tabulated below. Included also is NOEL reported for Varisoft 445.

Exposure Duration	*Highest Dose Tested*	*NOEL (systemic effects)*
14 days 7 hours, 5 days/week*	600 mg/kg bwt	600 mg/kg bwt/day
91 days 7 hours, 5 days/week**	27 mg/kg bwt	27 mg/kg bwt/day
91 days 7 hours, 5 days/week*	300 mg/kg bwt	300 mg/kg bwt/day
91 days 7 hours, 5 days/week*	400 mg/kg bwt	400 mg/kg bwt/day
91 days 7 hours, 5 days/week* *Varisoft 445*	300 mg/kg bwt	300 mg/kg bwt/day

*Source: (FSQSC 1988)
** Source: (TSCATS 1988)

9.5 Reproductive and Developmental Effects (Dynamic Corporation 1987)

Notified Chemical: test not conducted.

Analogue: The following data for Varisoft 445 were provided in summary form.

Varisoft 445 (78% active) was administered to rats by gavage at dose levels of 200 or 600 mg active compound/kg bwt, daily from days 6 to 12 or 15 of gestation. No maternal deaths occurred. A decrease in food consumption was observed during the first three days in the high dose animals. Overall reproduction parameters and pregnancy rates were unaffected. The incidences of skeletal and soft-tissue defects were not significantly different between treated and control animals. The NOEL for both maternal and developmental toxicity was reported as 600 mg/kg bwt/day.

9.6 Genotoxicity

9.6.1 *Salmonella typhimurium* Reverse Mutation Assay (Jagannath DR 1989)

Test Substance(analogue):	Varisoft 475 (75%)
Strains:	TA 1535, TA 1537, TA 1538, TA 98, TA 100
Metabolic Activation System:	S9 fraction derived from the liver of rats pretreated with Aroclor 1254
Concentration range:	0.05 µL - 8.0 µL, DMSO solvent
Test method:	similar to OECD TG 471
Result:	Varisoft 475 (75%), with or without S9 metabolic acivation, was not mutagenic to the strains tested

9.6.2 *In Vitro* Chromosomal Aberration Assay in Chinese Hamster Ovary Cells (Murli H 1989)

Test Substance(analogue):	Varisoft 475 (75%)
Cells:	Chinese hamster ovary (CHO)
Metabolic Activation System:	S9 fraction derived from the liver of rats pretreated with Aroclor 1254
Doses:	without metabolic activation: test substance 3.74 - 74.8 µg/mL, positive control cyclophosphamide; with metabolic activation: test substance 15.0 - 199 µg/mL, positive control mitomycin C ;
Test method:	similar to OECD TG 473
Result:	Varisoft 475 (75%), with or without S9 metabolic

activation, did not induce a significant increase in chromosomal aberrations in CHO cells

9.6.3 Unscheduled DNA synthesis (FSQSC 1988)

Analogue: The following data for Varisoft 445 were provided in summary form.

In assays conducted by three separate testing laboratories, Varisoft 445 was considered negative for Unscheduled DNA Synthesis (UDS) in WI-38 human diploid fibroblasts, with and without metabolic activation. One laboratory in repeating the test found a positive response for UDS, without metabolic activation. This positive response was considered to be an isolated finding as it was not repeatable, not dose responsive and spurious.

9.7 Overall Assessment of Toxicological Data

The notified chemical in Varisoft 3690, is a UVCB (chemical of unknown, or variable composition or biological origin).

The notifier supplied toxicological data for the acute oral toxicity and the skin and eye irritation potential of the notified chemical. In these tests the notified chemical was tested at varying percent solids. The notifier states that no acute dermal or inhalation toxicity studies or sensitisation, repeat dose and genotoxicity studies have been conducted on Varisoft 3690 and a variation of the schedule requirements was claimed and accepted on the basis that analogue data was provided. For the skin sensitisation, repeat dose and genotoxicity schedule requirements, the notifier provided data from tests conducted on analogues including Varisoft 475. Results (in summary form) from a pharmacokinetic study and reproductive and developmental study on Varisoft 445 were also provided in the submission.

Varisoft 3690 is stated to vary from the existing chemical Varisoft 475 on the basis of the source of the fatty acid component. The notifier claims that the toxicity of Varisoft 475 would be very similar to that of the notified chemical. The three Varisoft chemicals (445, 475 and 3690) are imidazolium quaternary ammonium compounds, are chemically similar and can be considered analogues of each other for the purposes of toxicological evaluations.

Pharmacokinetic studies reveal that Varisoft 445 is very poorly absorbed from the gastrointestinal tract or dermally and what little is absorbed is rapidly excreted via renal and biliary mechanisms. Some retention by tissue occurs, less than 0.4% following dermal application or less than 5% following oral administration. From these investigations it would appear that imidazolium quaternary ammonium compounds will not accumulate in the body to any significant extent as a result of repeated ingestion or dermal contact.

The notified chemical when tested at 5% and 76% solids was of very low acute oral toxicity with an LD_{50} greater than 20 000 mg/kg. A minimum lethal dose of greater than 1.8 gram active compound per kg was determined in a dermal toxicity test with Varisoft 475. In the pharmacokinetic study in rats, radiolabelled Varisoft 445 was poorly absorbed through the dermal route, and a small amount of radioactivity was found in all body tissues. It is likely the notified chemical will also be poorly absorbed percutaneously and therefore of low acute dermal toxicity.

Due to the defatting action of imidazolium quaternary ammonium compounds, dermal

irritancy is associated with the notified chemical and its analogues (see repeat dermal studies below). The severity of the irritancy would appear to be concentration dependent as manifested in the following studies with the notified chemical. Skin irritation studies were performed with different concentrations (5%, 76% or 90%) of the notified chemical. At a concentration of 90%, the notified chemical was severely irritating to the skin of rabbits, producing moderate to severe erythema and severe oedema in some test animals. Dilution of the notified chemical to a concentration of 76% or 5% diminished the extent of irritation, with slight to moderate and slight irritation being observed after a 4-hour exposure period, respectively. Humans would appear to be less susceptible to the irritancy of the analogue as no skin irritation was observed with Varisoft 475 at 5% w/v.

The notified chemical at 90% caused severe ocular lesions, which progressed throughout the 7-day observation period. The notified chemical at 76% was reported corrosive to rabbit eye at the 72-hour observation time. At 5% the notified chemical was a slight eye irritant with effects limited to the conjunctiva.

The notifier submitted non-adjuvant skin sensitisation data for the analogue substance Varisoft 475, which showed that it was not sensitising to guinea pig skin at very low induction (1%) and challenge (1%) concentrations. However, when an induction concentration of 25% and a 5% challenge concentration were used in a non-adjuvant type test, 17 out of 20 animals showed evidence of sensitisation. In human patch test studies, using a very low induction and challenge concentrations (0.25% for both) of Varisoft 475, none of the volunteers showed evidence of sensitisation. On the basis of these findings and the low concentrations tested, the skin sensitisation potential of the notified chemical, Varisoft 3690, cannot be discounted.

No repeat dose toxicity data were submitted for the notified chemical, though repeat dose test have been carried out on the analogue Varisoft 475. Oral repeat dose tests have been conducted on dogs and rats using Varisoft 475. In a two week palatability study in dogs, up to 30 000 ppm of Varisoft 475 was administered in the diet. Clinical observations included decreased food consumption and weight loss initially, and soft stools and/or diarrhoea noted on several occasions in higher dose groups. In a four week study in rats, minor changes in serum enzymes and bilirubin were reported at 100 mg/kg bwt/day, the highest dose tested. The NOEL reported for this study was 100 mg/kg/day. In a 13 week study in rats, changes in serum chemistry and liver weights were noted in males receiving Varisoft 475 at 1 000 mg/kg bwt/day but this was not accompanied by histopathologic evidence of hepatic injury. No treatment related findings were found in the bone marrow and the NOEL was determined at 100 mg/kg bwt/day. In both studies the NOEL is similar with no evidence of a tendency to increased toxicity with increased duration of the study. Based on the findings of repeat dose testing with the analogue Varisoft 475 and pharmacokinetic studies on Varisoft 445, it is expected the notified chemical will be poorly absorbed across the gastrointestinal tract, rapidly excreted and any amount absorbed will not result in any significant toxicity or accumulation in the body following repeated exposure.

Other than skin lesions, no treatment related changes were observed in 2 or 13-week dermal repeat dose study in rabbits using Varisoft 475 or 445. The NOELs reported for each study represented the highest dose tested. As above, based on the findings of repeat dose testing with Varisoft 445 and Varisoft 475 and pharmacokinetic studies on Varisoft 445, it is likely the notified chemical will be poorly absorbed dermally and any amount absorbed will be rapidly excreted. Significant toxicity or accumulation in the body following repeated dermal

exposure is not expected.

Varisoft 445 tested at 600 mg of active compound/kg bodyweight did not cause maternal or developmental toxicity in rats.

From the above findings on Varisoft 475 and Varisoft 445, the notified chemical would not be expected to be absorbed significantly via the oral or dermal route, accumulate in the body to any significant extent or exhibit biological effects dissimilar to those of the analogues. It should be noted that because the notified chemical is a skin irritant in animals, repeated dermal exposure may cause the barrier function of the skin to be compromised and therefore facilitate penetration of the notified chemical into the circulation. However, the results of repeat dermal studies with Varisoft 475 and Varisoft 475 indicate that dermal absorption is not associated with significant toxicity.

Varisoft 475, was not mutagenic *in vitro* in studies using bacteria or mammalian cell lines. Varisoft 445 was not considered mutagenic in the Unscheduled DNA Synthesis assay. No *in vivo* studies were provided. The notified chemical would not be expected to be mutagenic.

The notified chemical at the 90% solids was a moderate to severe skin irritant and severely irritating to eyes. By analogy with Varisoft 475, the notified chemical has potential for skin sensitisation. Based on these findings the notified chemical would be classified as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 1999). The overall hazard classification for health effects for Varisoft 3690 is Harmful (Xn), with risks phrases, R43 – May cause sensitisation by skin contact, R41 – Risk of serious damage to eyes, and R38 – Irritating to skin, assigned.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The following ecotoxicity data has been supplied for the notified chemical, Varisoft 3690, by the notifier. The data was supported by test reports and are summarised below.

Test	*Species*	*Results*	*Reference*
acute toxicity: semi static 96 hour concentrations[a]: 0.32, 1.0, 1.8, 3.2, 5.6 mg/L	Golden orfe (*Leuciscus idus*)	1.8 < LC_{50}< 3.2 NOEC = 1.8	(Hill RW 1983)
acute toxicity: static 48 hour concentrations[a]: 0.018, 0.032, 0.056, 0.10, 0.18, 0.32 mg/L	Water flea *(Daphnia magna)*	EC_{50} = 0.087 (CI 0.075 – 0.10) NOEC = 0.056	(Williams TD Thompson 1983)
static 72 hour growth inhibition concentrations[a]: 0, 0.010, 0.030, 0.063, 0.125, 0.250, 0.500 mg/L	Algae (*Selenastrum capricornutum*)	E_rC_{50} = 0.33[b] (CI 0.27 – 0.41) NOEC = 0.03 LOEC = 0.0625 E_bC_{50} = 0.14[c] (CI 0.00 – 0.19) NOEC = 0.03 LOEC = 0.0625	(Stauber J Adams M 1998)

NOEC - no observable effect concentration, LOEC - lowest observable effect concentration.
[a] Nominal concentrations; [b] Calculated by Stauber and Adams; [c] Calculated for this assessment.

No mortalities were observed throughout the fish study at concentrations below 1.8 mg/L. After 24 hours, 30% mortality was observed at 3.2 mg/L. This had increased to 100% by 48 hours. At 5.6 mg/L 100% mortality was observed after 24 hours. Hence, probit analysis is not possible and the 96 hour LC_{50} for Golden orfe is between 1.8 and 3.2 mg/L. No observations of sublethal effects were made during the study.

In the daphnia study, immobilisation was not observed at or below 0.032 mg/L. A single daphnia was immobilised in one of the 0.056 mg/L treatments after 24 hours with no further immobilisation observed at 48 hours. No immobilisation was observed at 0.10 mg/L after 24 hours. At 48 hours, 70% immobilisation was observed at 0.10 mg/L. At the two highest concentrations, 50% immobilisation was observed after 24 hours, increasing to 100% by 48 hours. The EC_{50} was determined by probit analysis. Once again no observations of sublethal effects were made during the study.

In the algal toxicity study provided, an E_rC_{50} of 0.33 mg/L was calculated from the slope of the growth curves at the various test levels using a Trimmed Spearman-Karber calculation with ToxCalc version 5.0. An analogous calculation for this assessment using the raw slope data provided by the notifier obtained the same endpoint of 0.33 mg/L. However, the 95% confidence limits were 0.08-1.38 mg/L, significantly different from that quoted in the test report. An E_bC_{50} of 0.14 mg/L was also calculated for this assessment from the cell count data in the test report using linear interpolation with 80 resamples.

The ecotoxicity data provided for the notified substance indicates that it is very highly toxic to aquatic invertebrates, highly toxic to algae and moderately toxic to fish.

No chronic data has been supplied by the notifier. It should be noted that the US EPA assumes an acute to chronic ratio of greater than or equal to 10 for fish and daphnia for cationic surfactants (Nabholz JV Miller P Zeeman M 1993).

In addition to the above data, the following ecotoxicity results have been supplied for the analogue product Varisoft 475. The two substances differ in the ratios of the fatty acids used to form the alkyl chains. The results for Varisoft 475 are summarised below. Only a simple listing of results and no other information was supplied.

Fish

Test	*Species*	*Results mg/L*	*Reference*
acute toxicity:			
96 hour[a]	Bluegill sunfish (*Lepomis maccrochirus*)	LC_{50} = 1.0 - 2.2	(Dynamic Corporation 1987)
96 hour[b]		LC_{50} = 65	(FSQSC 1988)
96 hour[c]		LC_{50} = 58 - 82	(Dynamic Corporation 1987)
acute toxicity: 96 hour[d]	Sheepshead minnow (*Cyprindon variegatus*)	LC_{50}> 1 000	(FSQSC 1988)

a laboratory water
b river water
c laboratory water and equimolar anionic surfactant, linear alkyl benzene sulfonate (LAS) or river water without added silt/sediments
d marine water

Aquatic Invertebrates

Test	*Species*	*Results mg/L*	*Reference*
acute toxicity:			
48 hour[a]	Water flea (*Daphnia magna)*	LC_{50} = 0.1	(Dynamic Corporation 1987)
48 hour[b]		LC_{50} = 22	(FSQSC 1988)
48 hour[c]		LC_{50} = 22	(Dynamic Corporation 1987)
96 hour[d]	Mysid Shrimp	LC_{50} = 1.5	(FSQSC 1988)
96 hour	Pink Shrimp	LC_{50} = 55	(Dynamic Corporation 1987)

a laboratory water
b river water
c surface water
d marine water

Algae

Test	*Species*	*Results mg/L*	*Reference*
algistatic[a]	Selenastrum sp	algistatic conc. = 0.037	(Dynamic Corporation 1987)
algistatic[b]	Selenastrum sp	algistatic conc. = 2.4	
algistatic[a]	Microcystis sp	algistatic conc. = 0.23	
algistatic[a]	Dunaliella sp	algistatic conc. = 6.1	

a algal assay procedure medium
b algal assay procedure medium and equimolar LAS

The ecotoxicity data for Varisoft 475 indicate that it ranges from highly toxic to practically non toxic to fish, highly toxic to slightly toxic to aquatic invertebrates and very highly toxic to moderately toxic to algae.

The notified chemical has been subject to a Ministerial exemption (Section 30 of the Act) and was used at the pulp and paper mill at half the proposed initial rate during the period of March-September 1997 (note that the rate has been reduced to one third of the initial proposed rate). The mill conducts regular ecotoxicity testing on the discharge from their main drain for Rainbow Trout, *Daphnia carinata* and luminescent bacteria. The results of the samples taken between March and September 1997 are summarised below.

Test	*Species*	*Result*		
		17 March 1997	*2 July 1997*	*30 September 1997*
15 minute	Microtox (luminescent bacteria)	No Observed Acute Toxicity	No Observed Acute Toxicity	No Observed Acute Toxicity
96 hour acute	Rainbow Trout (*Oncorhynchus mykiss*)	No Observed Acute Toxicity	No Observed Acute Toxicity	No Observed Acute Toxicity
48 hour acute	Water flea *(Daphnia carinata)*	No Observed Acute Toxicity	No Observed Acute Toxicity	No Observed Acute Toxicity

These studies were based on OECD (Organisation for Economic Co-operation and Development 1995-1996) and US EPA Test Guidelines (United States Environmental Protection Agency 1985). In the daphnia and fish tests, test organisms were exposed to undiluted effluent samples from the main drain into the receiving waters effluent samples diluted to 50 and 25% with soft water and a control. The luminescent bacteria were exposed to four dilutions of the effluent (10, 20, 40 and 80%). No attempt was made to determine the concentration of the notified chemical in any of the samples.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The majority of the notified chemical is expected to share the fate of the facial and toilet tissues to which it is adsorbed. These will be used Australia wide and either be consigned to landfill (facial tissues) or discharged to the sewer (toilet tissue). In the sewer the notified substance is expected to partition with the toilet tissue to the sewage sludge. Sludge from sewage treatment plants is expected to be placed in landfill or incinerated. Incineration of the notified chemical will result in its degradation to give water and oxides of carbon and nitrogen.

Based on an annual quantity of municipal solid waste of 13 million tonnes, the average concentration of the notified substance entering landfill from the disposal of facial tissues would be less than 0.6 ppm (0.6 tonnes/month × 12 /13,000,000 tonnes). The average concentration of the notified substance in the sewer as a result of the disposal of toilet tissue is approximately 1 ppb (assuming 150 L per capita water usage for an Australian population of 18 million people and a monthly discharge of 1.1 tonnes of the notified substance to sewer bound to toilet tissue). The above concentrations in landfill and sewer from facial and toilet tissues assume 99% adsorption to the cellulose fibres during paper manufacture.

The release of the notified chemical with the greatest potential for environmental impact is the discharge of the waste water from the pulp and paper mill. The notified substance is added during the wet processing of the cellulose fibres. The paper mill uses ground water for processing. Waste from the processing passes through the on-site treatment works consisting of a primary clarifier and a series of three aerobic degradation ponds. The treated effluent then passes into an 11 km drain before discharging into the receiving waters. The flow in the drain is significant and contains little sediment. Hence, adsorption in the drain is unlikely to reach equilibrium and the adsorption rate in the drain is likely to be lower than the 50-90% assumed by the US EPA (Boethling RS Nabholz JV 1997). Additionally, it is possible that with continual discharge of the notified substance that the adsorption sites within the drain will be exhausted further diminishing the adsorption rate. Therefore, a conservative estimate of half the US EPA adsorption rates range has been used in estimating the potential environmental hazard.

The notifier provided a receiving waters management plan, prepared in November 1996 for the relevant State Authority (reference undisclosed). The receiving waters are dune bound and the water level is managed in such a way as to minimise the need for marine discharge – release to the marine environment has occurred only twice in the last decade. Mixing in the lake is not efficient as evidenced by the measurement of faecal coliform levels around the drain (faecal coliforms are also discharged in paper mill effluent). The concentration of bacteria decreases rapidly with distance from the drain. Additionally, it is anticipated that the evaporation rate from the lake surface would be significant and possibly comparable with the rate of influx of discharge from the plant, creating an essentially static system. The above information has been used to calculate Predicted Environmental Concentrations (PECs). Calculations of the best and worst cases are outlined below.

Best Case (90% adsorption)

Usage of the notified substance:	1,920 kg/per month
Treatment plant flow rate:	50 ML per day
Adsorption to paper during manufacture:	99%
Removal during on site treatment:	90%
Adsorption in Drain:	45%
Dilution factor in receiving waters:	5
Removal by dissolved organic carbon in lake:	90%
Predicted Environmental Concentration (PEC):	**0.01 µg/L (ppb)**

Worst Case (50% adsorption)

Usage of the notified substance:	1,920 kg/per month
Treatment plant flow rate:	50 ML per day
Adsorption to paper during manufacture:	99%
Removal during on site treatment:	50%
Adsorption in Drain:	25%
Dilution factor in receiving waters:	5
Removal by dissolved organic carbon in lake:	50%
Predicted Environmental Concentration (PEC):	**0.40 µg/L (ppb)**

The PECs above represent the concentration entering the lake on a daily basis. The continual discharge of the notified chemical into the lake will result in a build up in the concentration of the notified chemical mitigated by its breakdown. For a continuous discharge and steady degradation a steady state concentration (C_{ss}) will be reached as given by the following equation:

$$C_{ss} = k1/k2$$

where k1 is the entry rate and k2 is the degradation rate (ln 2/environmental half-life).

A report (FSQSC 1988) submitted by the notifier used an environmental half-life of 30 days for IQAC (Varisoft 475) and EQACs (ethoxylated quaternary ammonium compounds) to calculate the steady state concentration for the release of these compounds into a river basin system of the United States. Assuming a 30 day environmental half-life, the notified substance would reach steady state concentrations in the lake of 0.5 ppb and 17.3 ppb. The worst case PEC of the notified substance is around 20% of the concentration shown to be acutely toxic to *Daphnia magna*. It is also around one eighth of the concentration shown to be toxic to algae (based on the E_bC_{50} calculated by for this assessment).

Given that the notified chemical is not readily biodegradable the environmental half-life of the substance may be longer than 30 days. For an environmental half-life of 90 days the steady state concentrations would be 1.5 ppb and 52 ppb for the best and worst case

adsorptions, respectively. Therefore, the worst case predicted steady state concentration in the lake may present an unacceptable environmental hazard to both daphnia and algae. Furthermore, in the best case concentration, potential environmental hazard is also marginal. While the safety factor for daphnia is about 60, this does not take chronic toxicity into account, which would lower this at least to single figures.

The notifier has provided toxicity data for rainbow trout and daphnia when exposed to the discharge from the main drain from the plant when the substance was used under the Section 30 Permit. Although the rate of substance use during this period was comparable with that proposed, the tests do not take into account the effect of continual discharge of the substance as test organisms were only exposed to the concentration of the notified chemical in the effluent.

However, the toxicity profile for the analogue, Varisoft 475, suggests that natural waters significantly moderate the toxicity of the substance. Some degree of moderation has been taken into account in evaluating the potential environmental hazard for the notified substance by assuming a percentage is adsorbed to DOC. The effect of this moderation is well below that observed for Varisoft 475. However, without full details of the ecotoxicity studies for Varisoft 475, it is difficult to justify a higher level of moderation for the notified chemical.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Based on toxicity studies submitted on Varisoft 3690 and the claimed analogue Varisoft 475, the notified chemical is moderate to severely irritating to the skin (4 hour contact time with a 90% preparation), a severe irritant to the eyes (90% preparation, not rinsed), and a potential skin sensitiser. It is not genotoxic and has low oral toxicity with an LD_{50} of greater than 20 000 mg/kg. Skin sensitisation studies with Varisoft 475 in humans, did not find evidence of skin sensitisation. No treatment related findings were reported either in repeat-dose tests or a reproductive and developmental test. Based on the skin and eye effects and skin sensitisation potential, the notified chemical would be classified as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 1999). The overall hazard classification is Harmful (Xn) with risk phrases: R43 - May cause sensitisaton by skin contact; R41 - Risk of Serious Damage to Eyes; and R38 - Irritating to Skin.

Occupational Health and Safety

The notified chemical will not be manufactured in Australia but imported in 1 000 L poly-Schutz containers. No reformulation will occur following import.

Waterside, transport and storage workers are not expected to be exposed to Varisoft 3690, under normal conditions of handling, therefore the occupational risk posed to these workers is negligible.

During paper manufacture, the addition of Varisoft 3690 to cellulose fibres occurs by way of an automated process as the chemical is directly pumped from import containers to the storage tank and from the storage tank to the pulp mixture. Dermal and ocular exposure to drips and spills may occur when connecting/disconnecting any of the transfer lines or when measuring

the flow rate. The notifier states that personal protective equipment is used as required. This will serve as an additional mechanism to control exposure to the notified chemical. The notifier states that work related injuries or diseases arising from exposure to the notified chemical have not been encountered. Given the short duration of the transfer and metering activities and use of personal protective equipment, the risk of skin and eye irritation is expected to be low. Some risk of skin sensitisation may exist for process workers repeatedly exposed to the notified chemical, albeit for short, infrequent periods.

There is expected to be negligible risk of adverse health effects posed to winder operators coming into contact with treated tissue paper because at this stage of operations, the notified chemical is strongly bound to the cellulose fibres preventing substantial transfer of the notified chemical to the skin.

For maintenance workers exposure is also expected to be negligible given that the majority of the notified chemical is bound to fibre and that exposure to any residual chemical, will be of minimal duration and frequency (as required, two minutes per week). In addition, personal protective equipment would be expected to be worn and special isolation procedures are in place before maintenance workers attend to any plant equipment. Therefore, the health risk to maintenance workers arising from exposure to the notified chemical is low.

The notified chemical is a Class 3 (Flammable) Dangerous Good (Federal Office of Road Safety 1998). The notifier states that the chemicals used in paper tissue manufacture are stored in bunded, well-lit, and well ventilated areas and are all labelled appropriately. These areas are separate from the main manufacturing area and workers only enter when necessary to check, make adjustments, or refill storage tanks. All workers receive education and training for the safe use and handling of chemicals and competent operation of plant equipment. Every operating position of the machine has a fully documented training manual, and each machine has a trainer who is responsible for ensuring that all personnel on the machine have achieved minimum standards of competency.

Varisoft 3690 contains the solvent isopropanol. Employers are required to ensure the NOHSC exposure standard for isopropanol, 400 ppm TWA, 500 ppm STEL (NOHSC 1995) is not exceeded in the workplace.

Workers should be instructed to follow good hygiene practices to control dermal exposure to Varisoft 3690 and to remove any chemical that has come into contact with the skin as soon as practicable with plenty of water. Workers should be advised of the potential for occupational dermatoses following repeated skin exposure to Varisoft 3690 and to report any skin changes to the occupational health and safety officer at their workplace. Further guidance on preventing the occurrence of occupational skin diseases can be found in the NOHSC guide *Occupational Diseases of the Skin* (NOHSC 1990).

These work place procedures and controls will also serve to control exposure to the notified chemical.

The health risk to workers who routinely use tissues in their work is negligible as the notified chemical is strongly bound to the fibres and therefore not bioavailable.

Public Health

The primary hazard associated with the use of this chemical in toilet and facial tissues is the direct skin and eye irritation. Although public exposure will be widespread and the notified chemical is not without significant acute topical toxicity, the exposure to this compound will be low and the primary hazards identified are unlikely to be relevant at the low concentration present in processed toilet or facial tissues. Varisoft 3690 is present at approximately 0.2% in the product and is strongly bound to the fibres of the tissue, preventing transfer of the notified chemical to the skin. Assessments of similar compounds applied to clothing as fabric softeners, provided by the applicant, estimated the daily transfer rate at 0.07 mg/kg bw/day in adults on a clothing content of 270 mg/m^2. As a skin contact time for toilet and facial tissues is considerably shorter than for clothing, the transfer rate is likely to be commensurately lower.

13. RECOMMENDATIONS

1. To minimise occupational exposure to Varisoft 3690, in particular skin and eye contamination the following guidelines and precautions should be observed:

- Safety goggles should be selected and fitted in accordance with Australian Standard (AS) 1336 (Standards Australia 1994) to comply with Australian/New Zealand Standard (AS/NZS) 1337 (Standards Australia/Standards New Zealand 1992);

- Industrial clothing should conform to the specifications detailed in AS 2919 (Standards Australia 1987) and AS 3765.1 (Standards Australia 1990);

- Impermeable gloves or mittens should conform to AS 2161.2 (Standards Australia 1998);

- All occupational footwear should conform to AS/NZS 2210 (Standards Australia/Standards New Zealand 1994);

- Spillage of the notified chemical should be avoided. Spillages should be cleaned up promptly with absorbents which should be put into containers for disposal;

- Workers should be instructed to follow good hygiene practices to control dermal exposure to the notified chemical and to remove any notified chemical that has come into contact with the skin as soon as practicable with plenty of water. 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 the occupational health and safety officer at their workplace. Further guidance on preventing the occurrence of occupational skin diseases can be found in the NOHSC guide Occupational Diseases of the Skin (NOHSC 1990); and

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

2. This assessment indicates that the notified substance could potentially present a hazard to the environment when it used at the proposed rate. However, this hazard may be mitigated by the effect of natural waters on the toxicity of the notified chemical. It is recommended that the notifier provides, on an annual basis to the Director, the following data which pertains to the end user's plant:

- Results of biological assays of the lake water close to the inlet using chronic daphnia testing to monitor the effects of the possible build-up of notified chemical in the receiving water (as a result of the continual discharge of the substance to the receiving water); and

- Results of biological assays from the monitoring of the toxicity of the effluent from the main drain.

14. MATERIAL SAFETY DATA SHEET

The Material Safety Data Sheet (MSDS) for Varisoft 3690 was provided in a format consistent with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 1994).

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

Secondary notification under Section 64(1) of the Act will be required if:

- the method of use changes in such a way as to further increase the environmental exposure of the notified chemical (for example, the use of the notified chemical at another site), particularly to natural waters;
- testing close to inlet waters indicate chronic effects on daphnia; or
- information becomes available on adverse environmental effects of the notified chemical.

Secondary notification of the notified chemical under subsection 64(2) of the Act shall be required if any of the circumstances stipulated in that subsection arise.

Should the Director require the secondary notification of this chemical, the following information is likely to be required (particularly if lake water testing indicates chronic daphnia toxicity):

- chronic daphnia testing of the notified chemical;
- aquatic toxicity studies conducted in natural waters to investigate the possible mitigation of the toxicity through sorption to suspended matter; and
- specific degradation data to model expected degradation once it is diluted and mixed. The data should be generated in a study undertaken according to international guidelines, where the degradation of the notified chemical has been followed using HPLC or ^{14}C radiolabeled chemical, and allow full elucidation of the degradation pathways.

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Attachment 1

The Draize Scale 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 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