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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

OGA 499

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

OGA 499

1. APPLICANT

Chevron Oronite Australia of 385 Bourke Street MELBOURNE VIC 3000 (ARBN 001 010 037) has submitted a standard notification statement in support of their application for an assessment certificate for OGA 499.

2. IDENTITY OF THE CHEMICAL

The chemical name, CAS number, molecular and structural formulae, details of the polymer composition have been exempted from publication in the Full Public Report and the Summary Report.

Marketing Name:	OGA 499
Other Names:	CP 2043; SP 2043; OLOA 2509U.
Number-Average Molecular Weight (NAMW,M_n):	2 146
Weight-Average Molecular Weight (M_w):	2 293
Maximum Percentage of Low Molecular Weight Species	
Molecular Weight < 500:	0
Molecular Weight < 1 000:	0.32
Polydispersity (M_w/M_n):	1.07
Method of Detection and Determination:	IR analysis; ^{13}C NMR

Comments on Chemical Identity

A GPC (Gel Permeation Chromatography) trace and printout was supplied to determine the NAMW and percentage of low molecular species. An IR (Infrared) chromatograph was also submitted for the identification of the notified substance.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C & 101.3 kPa:	Colourless to yellowish viscous liquid
Boiling Point:	Decomposes before boiling
Specific Gravity:	0.968 g/mL at 15°C
Vapour Pressure:	< 1.33 x 10^{-3} kPa at 25°C
Water Solubility:	< 1 ppm
Partition Co-efficient (n-octanol/water):	log P_{ow} >7.6
Kinematic Viscosity:	275 x 10^{-6} m^2/sec at 40°C
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)
Flash Point:	>200°C
Flammability Limits:	Combustible will not burn unless preheated
Autoignition Temperature:	> 200°C
Explosive Properties:	Not known to be explosive
Degradation Products:	Stable under normal conditions
Loss of Monomers, Additives, Impurities:	None expected
Particle Size:	Polymer is a viscous liquid and unlikely aerosols of inspirable size will be generated under forseeable uses

Comments on Physico-Chemical Properties

The boiling point of the notified polymer was not determined. The notifier estimates that the polymer will have a low vapour pressure.

The water solubility of the notified polymer was not determined. However, the notifier indicates that the butyl groups of the polyether make the notified polymer very insoluble in water. The polymer is expected to have a water solubility of about 1 mg/L.

Due to the low water solubility of the notified polymer hydrolysis is unlikely in the environmental pH range of between 4 and 9. Also the notified polymer contains no functional groups that can hydrolyse.

The partition coefficient log P_{OW} of OGA 499 between n-octanol and water was estimated to be greater than 7.6 at 20°C by a flask shaking method using reverse phase HPLC similar to the test OECD TG 107.

The determination of the adsorption/desorption coefficient of the notified polymer was not undertaken. The notified polymer is expected to be insoluble in water and will largely partition into *n*-octanol rather than water. Due to its low water solubility and its high surface activity the polymer is expected to become associated with the organic component of soils and sediments. The notifier also indicates from studies of similar dispersant/detergent substances to the notified polymer that the adsorption/desorption binding coefficients are in the 40 to 50 000 range.

No dissociation constant data was provided for the notified polymer. At low pH the ω-amine functionality will be protonated, leading to increased water solubility.

4. PURITY OF THE CHEMICAL

Degree of Purity:	> 94%
Hazardous Impurities:	Exempt Information: Impurities are present at less than 0.5%
Non-hazardous Impurities (> 1% by weight):	Three impurities are each present at less than 2%.
Additives/Adjuvants:	None

5. USE, VOLUME AND FORMULATION

Use
The notified polymer, OGA 499, is intended for use as a deposit control detergent/dispersant additive in unleaded petrol. The notifier claims that the generalised effects of the use of OGA 499, when formulated in a deposit control additive package and subsequently used in a petrol engine are: reduced exhaust emissions; improved fuel economy; reduced engine deposits; and longer engine life.

Import Volume
OGA 499 will not be manufactured in Australia. It will be imported at up to 40% w/w in a pre-blended fuel additive in 8 000 L ISO containers. Import volumes are expected to reach a maximum of 500 000 kg per annum by the fifth year after introduction.

Upon arrival, the ISO tanks will be loaded and transported by road to approximately 5 petrol marketers.

Formulation
Blending of the fuel additive package containing OGA 499 into petrol will occur at approximately 20 petrol blending terminals. The final concentration of additive in fuel is 5 to 1 000 ppm.

6. OCCUPATIONAL EXPOSURE

Exposure
Dockside and Transport
The notified polymer will be imported in 8 000 L ISO containers. Occupational exposure is not likely except in the event of a spill.

Refinery/Terminal Facility
At the terminal facility the petrol additive is transferred from the import ISO containers (via flexible hosing) through hard piping to a storage tank. The components for petrol blends are drawn directly from their storage tanks *via* automatic computer controlled inline blenders and mixed before being sent to another storage tank. The additive is injected into unleaded petrol on a volumetric basis that will result in 5 to 1 000 ppm concentration in the final fuel. The blended petrol is transferred to tank trucks for distribution to petrol service stations.

During unloading of the ISO containers, opportunity for incidental[1] skin and eye contact to splashes and drips and spills exists as pump line connections between the ISO containers and storage container are being made or broken. The notifier estimates that spills and leaks are less than 50 grams per unloading operation. The notifier indicates one worker is involved in this activity.

[1] Incidental exposure is assumed to be one event per day and would typically involve splashes or spills which arose from the way in which the process was carried out. (European Commission (1996): Technical Guidance Document in Support of Commission Directive 93/67/EC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances - Part II, European Commission. Brussels.)

The level of workplace exposure during blending of the additive package to petrol is expected to be minimal because of the use of computer controlled automated processes and enclosed systems (in-line blenders).

Exposure to workers can occur during sampling for laboratory analysis of the additive package and the final fuel. Analysis is performed in the laboratory by one worker and takes several minutes.

Service Stations
Mechanics and service station personnel may be exposed to the very low concentration of notified polymer in the final fuel, during routine work procedures.

Control measures
Refinery workers will wear protective clothing, chemical goggles and rubber gloves. The notifier states that inspections of their customers sites have indicated that their blending facilities are well ventilated, with control systems for accidental spills and wastewater treatment. Transport workers are likely to have access to engineering controls and wear protective clothing. Auto mechanics and service station personnel are unlikely to wear gloves.

Worker Education and Training.
The pattern of use is considered as non-dispersive[2]. The notifier states the additive product containing OGA 499 will be handled by employees of major Australian petrol manufacturers. Workers involved in the above activities are knowledgeable of occupational health and safety aspects of petrol and would have received training in the handling of fuel and fuel additives.

7. PUBLIC EXPOSURE

It is expected that during transport, blending with petrol and storage, exposure of the general public to the notified polymer will be minimal, except in the event of an accidental spill. Prompt clean-up of releases and containment of spills will be required to prevent extensive contamination of soils, surface or ground water. Small spills are to be absorbed onto inert material or removed by pumping. Where feasible, contaminated soil is expected to be removed.

Public exposure to OGA 499 is expected to be occasional, but widespread as unleaded petrol containing the notified polymer will be sold to the public. Public exposure will occur when refilling petrol tanks either in automobiles or as petrol supplies for other uses, for example, mowers and garden equipment. The most likely routes of exposure are by dermal, inhalation and possibly ocular.

[2] Non dispersive use refers to processes in which substances are used in such a way that only certain groups of workers, with the knowledge of processes, come into contact with these chemicals. Procedures are normally worked out to achieve adequate control of exposure commensurate with risk. (Ibid.)

8. ENVIRONMENTAL EXPOSURE

After importation by sea the polymer will be transported *via* road without repackaging in the closed 8 000 L isotanks; potential release would only be through accidental spills. The MSDS details procedures to enable clean up operators to protect the environment in these cases. Once received by the customers, the isotanks are emptied *via* a 2 to 2.5 metre flexible hose. After the isotank is unloaded the hose is automatically pigged to the isotank. The notifier indicates that during this procedure the amount of material lost due to spills and leaks is less than 50 mL per load, or 5 to 45g of the notified polymer.

The empty isotanks are not cleaned in Australia, but shipped back to the USA. It is presumed that the same 50mL volume of loss would occur at each similar transfer operation for example when transport tankers are filled with the final blended fuel product and at petrol service stations when tankers are emptied into storage tanks. In both these cases given its low percentage in fuel, the notified polymer loss during spills would be low.

Also no data is available that takes into account the frequent minor spills (less than one litre) that would occur at petrol bowsers as customers re-fuel their vehicles. However, given the low percentage in fuel, the loss of notified polymer in these spills would be low. The notifier also indicates that the spilt petrol will evaporate leaving the fuel additive containing the notified polymer behind. The notified polymer will bind strongly to the soil, concrete and asphalt. This coupled with the low water solubility of the polymer, means that consequent aquatic pollution should not be significant.

Environmental release will not be significant because the notifier claims that the polymer in the fuel additive is destroyed by combustion within the petrol engine. There is no direct data to support the claim and the notifier states that it is essentially an intuitive assumption. The polymer is made up of hydrocarbon and oxygen and a small amount of nitrogen, that is, the normal constituents of petrol. The notified polymer will be a minute part of the fuel and should not survive the temperatures at which the fuel is exploded within the internal combustion engine.

The notifier indicates that small amounts may make it into the crankcase of a combustion engine in blown-by gases. Once in crankcase used oil the notified polymer will continue to act as an ashless type dispersant providing increased performance.

The polymer and additive package will not be directly marketed to the public, but preblended into the petrol prior to transport and retail at service stations.

Fate

If the polymer is released to soil in either a spill or leak from a storage tank, it is expected to bind strongly to soil due to its low water solubility and high partition coefficient of greater than 7.6. If released to an aquatic environment, the polymer would tend to partition out of water and into sediment. Once adsorbed to soil/sediment, the fate of the polymer is unknown. However, the ready biodegradability of the notified polymer was examined by exposure to activated sewage sludge microorganisms at a concentration of 10 mg/L at 21°C for 28 days. Degradation of the notified polymer was assessed by the determination of carbon dioxide produced. A degradation of 50% was attained after 28 days (Safepharm Laboratories Limited 1998j) therefore the notified polymer cannot be considered to be readily biodegradable under the terms and conditions of the Modified Sturm Test OECD TG 301B.

The polymer is not expected to cross biological membranes, due to the low solubility and high molecular weight, and should not bioaccumulate (Connell 1990).

The notifier provides no data concerning the effect of the notified substance on tail pipe emissions. The notifier supplied a report published by the EPA (US EPA 1994) on the benefits of deposit control additives like the notified polymer OGA 499 in controlling tail pipe emissions and improving fuel economy. Discussions on test results provided show a positive statistical difference in HC, CO and NO_x emissions between test fuel with and without the additive. The long term result of detergent fuel additives is to reduce the formation of engine deposits, that is to both "keep clean" and "clean up" existing engine deposits leading to reduced levels of tail pipe emissions.

In combination with certain detergent/dispersant additives, the notified polymer is said by the notifier to be registered and approved for use with the US EPA as a fuel additive. Deposit control additives such as OGA 499 are said to be mandated by the US 1990 Clean Air Act because of their recognised ability to control the formation of port fuel injector deposits and intake valve deposits.

9. EVALUATION OF TOXICOLOGICAL DATA

Toxicity tests were performed in compliance with OECD/EEC Test Methods (European Commission 1992), (OECD 1995-1996) and according to OECD Principles of Good Laboratory Practices.

9.1 Acute Toxicity

Summary of the acute toxicity of OGA 499

Test	*Species*	*Outcome*
Acute oral toxicity	Rat	> 5 000 mg/kg
Acute dermal toxicity	Rat	> 2 000 mg/kg
Skin irritation	Rabbit	Slight to moderate irritant
Eye irritation	Rabbit	Slight irritant
Skin sensitisation:		
100% OGA 499 (SP2043)	Guineapig	Sensitising
85% OGA 499 (XF661*)	Guineapig	Non-sensitising
85% OGA 499 (OX15622**)	Guineapig	Sensitising
75% OGA 499 (OX15623)	Guineapig	Non-sensitising
50% OGA 499 (OX15624)	Guineapig	Non-sensitising
39% OGA 499 (OGA 600)	Guineapig	Non-sensitising
1% OGA 499 (OGA 600)	Guineapig	Non-sensitising
Repeat Insult Patch Test 0.2% OGA 499 (OGA 600)	Human	Non-sensitising

The name in parenthesis is the code for the various formulations containing the notified polymer.
* formulation containing notified polymer in light aromatic solvent naphtha.
** formulation containing notified polymer in Stoddard solvent & hydrotreated light distillates.

9.1.1 Oral Toxicity (Safepharm Laboratories Limited 1998c)

Species/strain:	Rat/Sprague Dawley Crl:CD
Number/sex of animals:	5/sex
Observation period:	15 days
Method of administration:	5 000 mg/kg bodyweight, (dose volume of 5.29 mL/kg)
Test method:	OECD TG 401
Clinical observations:	No signs of systemic toxicity noted
Mortality:	Nil
Morphological findings:	No abnormalities noted
LD_{50}:	> 5 000 mg/kg bodyweight
Result:	OGA 499 was of very low acute oral toxicity in rats.

9.1.2 Dermal Toxicity (Safepharm Laboratories Limited 1998b)

Species/strain:	Rat/Sprague Dawley CD
Number/sex of animals:	5/sex
Method of administration:	2 000 mg/kg (dose volume 2.12 mL/kg) held under semi occlusive dressing for 24 hours; after the treatment period, the dressing was removed and the treated site wiped clean with cotton wool moistened with liquid paraffin
Observation period:	14 days. The treated sites were observed for evidence of dermal irritation approximately 30 minutes after dressing removal and on Days 3, 7, 10 and 14
Clinical observations:	No signs of toxicity noted
Test method:	OECD TG 402
Mortality:	Nil
Morphological findings:	No abnormalities noted

Draize scores:

	Animal #									
	males					females				
Time after Treatment:	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***
Erythema										
30 minutes	1[a]	1	2	1	2	2	2	2	1	1
Day 3	0	0	0	0	0	2*	2**	1**	1	1**
Day 7	0	0	0	0	0	1	1	0*	0	0
Day 10	0	0	0	0	0	0	0	0	0	0
Oedema										
30 minutes	0	1	0	0	0	0	0	0	0	0
Day 3	0	0	0	0	0	0	0	0	0	0

[a] see Attachment 1 for Draize scales. * slight fissuring. ** moderate fissuring.

Dermal responses:
Slight or moderate erythema was noted at the treatment sites of all animals 30 minutes after dressing removal. Slight oedema was also noted at the treatment site of one male at this time. Slight or moderate erythema and slight or moderate fissuring were noted at the treatment sites of all females at Day 3. Slight erythema was noted at the treatment site of two females and slight fissuring was noted at the treatment site of one female at Day 7.
The treatment sites of males were normal at Day 3. The treatment sites of females appeared normal at Days 7 or 10.

LD_{50}: > 2 000 mg/kg bodyweight

Result: OGA 499 was of low dermal toxicity to the rat.

9.1.3 Inhalation Toxicity

Claims were made and accepted by the notifier for Variation of Schedule Requirements for this toxicological endpoint. OGA 499 is claimed not to be an inhalation hazard based upon its low vapour pressure. In addition, the high viscosity makes it unlikely that aerosols of inhalable size would be generated under normal use conditions.

9.1.4 Skin Irritation (Safepharm Laboratories Limited 1998a)

Species/strain:	Rabbit/New Zealand White
Number/sex of animals:	5 males and 1 female
Observation period:	1, 24, 48,72 and 96 hours post exposure
Method of administration:	0.5 mL of the neat test substance was introduced under a 2.5 x 2.5 cm cotton gauze patch on the dorsal skin of the rabbit and held in place under a corset; four hours after application residual test material was removed by gentle swabbing with cotton wool soaked in liquid paraffin. A contralateral area of untreated skin served as the control site.
Test method:	OECD TG 404

Draize scores:

Time after treatment	***Animal #***					
	1	***2***	***3***	***4***	***5***	***6***
Erythema/Eschar formation						
30 minutes	[a]2	2	2	2	1	2
24 hours	1	2	1	1	2*	2
48 hours	1	2	1	1	1	1
72 hours	0	1	0	1	0	0
96 hours	0	0	0	0	0	0
Oedema						
30 minutes	[a]1	2	1	1	0	1
24 hours	1	1	0	0	1	1
48 hours	1	1	0	0	0	0
72 hours	0	0	0	0	0	0
96 hours	0	0	0	0	0	0

[a] see Attachment 1 for Draize scales. * reaction extended up to 6 cm beyond treatment site.

Mean group score (24, 48 & 72 hour observation):	Erythema/Eschar Formation: 1 Oedema: 0.3
Comment:	Very slight to well-defined erythema and very slight to slight oedema was noted at all treated skin sites at 1, 24 and 48 hours. All treated skin sites appeared normal at 96 hours.
Result:	OGA 499 was slight to moderately irritating to rabbit skin.

9.1.5 Eye Irritation (Safepharm Laboratories Limited 1998e)

Species/strain:	Rabbit/New Zealand White
Number/sex of animals:	9 males
Observation period:	1, 24, 48 and 72 hours post instillation
Method of administration, Unirrigated eyes:	0.1 mL of the neat test substance was instilled into the conjunctival sac of the right eye of 6 rabbits; the left eye served as the control
Method of administration, Irrigated eyes:	0.1 mL of the neat test substance was instilled into the conjunctival sac of the right eye of 3 rabbits; after 30 seconds the eye was gently irrigated with 100mL of lukewarm water for one minute; the left eye served as the control
Test method:	OECD TG 405

Draize scores of nonirrigated eyes:

	Time after instillation											
Animal	***1 hour***			***24 hours***			***48 hours***			***72 hours***		
Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	1	1	2	1	1	0	1	0	0	0	0	0
2	2	2	2	1	1	1	0	0	0	0	0	0
3	2	1	1	1	0	0	0	0	0	0	0	0
4	1	1	1	1	0	0	0	0	0	0	0	0
5	1	1	2	0	0	0	0	0	0	0	0	0
6	1	1	1	0	0	0	0	0	0	0	0	0
Cornea	*All individual scores were zero*											
Iris	*All individual scores were zero*											

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

Mean scores for nonirrigated eyes:	Corneal opacity: 0.0 Iridial lesion: 0.0 Redness of conjunctivae: 0.3 Chemosis of conjunctivae: 0.2

Comment, Nonirrigated eyes:	Conjunctival irritation was noted in all treated eyes, and conjunctival chemosis and discharge was noted in one treated eye at 1 hour; all treated eyes appeared normal at 24 hours; no iridial or conjunctival effects were noted (all individual scores were zero)

Draize scores of irrigated eyes:

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

[1] see Attachment 1 for Draize scales

r = redness c = chemosis d = discharge

Comment, Irrigated eyes:	Conjunctival irritation was noted in all treated eyes at the 1 hour observation; Conjunctival redness persisted in one treated eye at 24 hours; No corneal or iridial effects were noted during the study (all individual scores were zero)
Result:	OGA 499 was very slightly irritating to rabbit eye.

9.1.6 Skin Sensitisation – Buehler Technique

The potential of the notified polymer, OGA 499, and formulations that contain it at varying concentrations, to produce delayed contact hypersensitivity in guineapigs was evaluated using the Buehler Method. In total, six studies were conducted, and all complied with the protocol recommended in OECD TG 406 (Buehler test).

Experimental Design and Methodology

In all studies a primary irritation study was conducted to determine the irritation threshold of the test substance for the purposes of determining the induction concentration (minimal irritant concentration) and challenge concentration (maximal sub irritant concentration). The irritation potential of the test substance at levels of neat test substance or test substance diluted in mineral oil at 50%, 25%, 10%, 5%, 2.5%, 1.0%, & 0.5% w/v was evaluated in two groups of four animals each. Four levels of the test substance were evaluated per animal such that each animal in a given group was exposed to the same levels. Results of the irritation screens are presented in Table 1. For the formulation identified as XF 661 (containing the notified chemical at 85%) the irritation study (Covance Laboratories Inc 1999a) was repeated for the neat test substance and at concentrations of 50, 25 and 10%, because of the dermal reactions observed in the first screen.

For the induction procedure, each test animal received a 6-hour occlusive application (using a Hill Top Chamber) of 0.3 mL of test substance to a clipped site on the animals back. The animals in the test group (20) received one application per week for 3 weeks for a total of three applications.

Two weeks following the administration of the third induction dose, a challenge dose of 0.3 mL of the test substance was administered on a previously untreated site on the test animals' back in the same manner as during the induction phase. At this time naïve control animals (10) were also treated in the same manner.

In some instances, a second challenge phase was conducted to further examine the sensitising potential of the test substance – a second challenge dose was conducted two weeks after the first challenge application, except for the study on 85% OGA in hydrocarbon solvent (Covance Laboratories Inc 2000a), where the 2nd challenge was conducted 3 weeks after the 1st challenge. Two new naïve sites were selected on each animal in the test group. In addition, 10 new naïve control animals were selected. Each animal in the test and additional naïve control group received a 0.3 mL dose of the test substance in the same manner as the first challenge application. The initial naïve control animals were not treated during this phase of the study.

Dermal responses were evaluated 24 and 48-hours after removal of the challenge patches and graded to a 5 point scale:

Grade 0	No reaction
Grade +/- or 0.5	Very faint erythema, usually nonconfluent
Grade 1.0	Faint erythema, usually confluent
Grade 2.0	Moderate erythema
Grade 3.0	Strong erythema, with or without oedema

Induction and challenge concentrations and dermal responses are presented in Table 2.

The criteria for a positive reaction - skin reactions of grade 1 or more are considered positive. The decision whether a test substance is a sensitiser is based on comparisons of results (incidence and severity) in test and naïve control animals.

Results:
SP2043 (100% OGA 499) is moderately to strongly sensitising to guineapig skin. OX15622, a formulation containing OGA 499 at 85% in a mixture of Stoddard solvent (CAS# 8052-41-3) & hydrotreated light distillates (CAS# 64742-47-8) is also moderately to strongly sensitising to guineapig skin. However, XF661 a formulation containing OGA 449 at 85% in light aromatic solvent naphtha (CAS# 64742-95-6) was not considered sensitising to guineapig skin under the conditions of the test. OX15623, OX15624, or OGA 600, formulations containing OGA 499 at 75%, 50%, or 39% in a mixture of Stoddard solvent & hydrotreated light distillates were not considered sensitising to guineapig skin under the conditions of the test. OGA 600, diluted to 1% OGA 499 in mineral oil was considered non-sensitising to guineapig skin under the conditions of the test.

TABLE 1 – RESULTS OF THE PRIMARY IRRITATION STUDY

Test substance identity & Formulation details	*Maximum Concentration Not Giving Rise To Irritating Effects*	*Remarks*
SP2043 100% OGA 499. (Hill Top Research 1997)	Not identified. At 0.5%, the lowest concentration tested, Grade 0.5 erythema was observed.	Very faint erythema reactions were observed with the neat test substance and at 2.5%, 1% & 0.5%. Very faint to faint reactions were observed at 50%, 25%, 10% & 5%.
XF661 85% OGA 499 in light aromatic solvent naphtha. (Covance Laboratories Inc 1999a)	Not identified. At 0.5%, the lowest concentration tested, Grade 0.5 erythema was observed.	During the second irritation study, very faint to moderate erythema reactions were observed at the sites treated with neat test substance and at 50%. Very faint erythema reactions were observed at one to three sites treated with either 10% or 25%. Very faint erythema reactions were observed at approximately the same incidence for all concentrations of test substance applied during the initial irritation study. Areas of subcutaneous haemorrhaging were also observed at one of the eight the test sites treated with neat test substance, and at one of the eight test sites treated at 50%.
OX15622 85 wt% OGA 499 in Stoddard solvent & hydrotreated light distillates (Covance Laboratories Inc 2000a)	25%	Very faint to faint erythema reactions were observed at sites treated with the neat test substances and at 50%.
OX15623 75 wt% OGA 499 in Stoddard solvent & hydrotreated light distillates (Covance Laboratories Inc 2000b)	5%	Very faint erythema reactions were observed at a minimum of one of the sites treated with 10 & 25%, and very faint to faint erythema reactions were observed at sites treated with the neat test substance and at 50%. Pinpoint areas of subcutaneous haemorrhaging were also observed at one site treated with the neat test substance.
OX15624 50 wt% OGA 499 in Stoddard solvent & hydrotreated light distillates (Covance Laboratories Inc 2000c)	10%	Very faint erythema reactions were observed at 3 of the 4 sites treated with 25%, very faint to faint erythema reactions were observed at 50%, and faint to moderate erythema reactions were observed at sites treated with neat test substance.
OGA 600 39% OGA 499 in Stoddard solvent, hydrotreated light distillates & 10% OGA 574 (Covance Laboratories Inc 1998b)	Not identified. At 0.5%, the lowest concentration tested, Grade 0.5 erythema was observed.	A faint erythema reaction was observed at one of the treated with 50%. No erythema was observed at 2.5% and 5%. Very faint erythema was observed on at leats one site of all other concentrations.
OGA 600 Diluted to 1% OGA 499 in mineral oil. (Covance Laboratories Inc 1998a)	25%	Faint erythema reactions were observed with the neat test substance and at 50%. Pinpoint areas of subcutaneous haemorrhaging were also observed at the test sites treated with neat test substance.

TABLE 2 – INCIDENCE OF DERMAL RESPONSES FOLLOWING CHALLENGE

Test substance identity & formulation details	*Induction Concentration*	*Challenge Concentration*	*Challenge*	*Animal*	*Incidence of Dermal Response Grades*										*Response*
					24 hour					*48 hour*					
					0	*0.5*	*1*	*2*	*3*	*0*	*0.5*	*1*	*2*	*3*	
SP2043 100% OGA 499. (Hill Top Research 1997)	SP2043 undiluted (100% OGA 499)	SP2043 undiluted (100% OGA 499)	1st	*Test*	0	5	9	5	1	0	1	8	10	1	Sensitising
				Naïve	0	10	0	0	0	1	9	0	0	0	
			Total No. of test animals with positive response:				*15/20*					*19/20*			
XF661 85% OGA 499 in light aromatic solvent naphtha. (Covance Laboratories Inc 1999a)	XF661 Undiluted (85% OGA 499)	10% XF661 in mineral oil (8.5% OGA 499)	1st	*Test*	12	8	0	0	0	9	8	1	1	0	Non-Sensitising
				Naïve	10	0	0	0	0	6	4	0	0	0	
			Total No. of test animals with positive response:				*0/20*					*0/20*			
		10% XF661 in mineral oil (8.5% OGA 499)	2nd	*Test*	15	5	0	0	0	15	4	1	0	0	
				Naïve	6	4	0	0	0	5	4	1	0	0	
			Total No. of test animals with positive response:				*0/20*					*1/20*			
		1% XF661 in mineral oil (0.85% OGA 499)	2nd	*Test*	20	0	0	0	0	20	0	0	0	0	
				Naïve	10	0	0	0	0	9	1	0	0	0	
			Total No. of test animals with positive response:				*0/20*					*0/20*			
OX15622 85 wt% OGA 499 in Stoddard solvent & hydrotreated light distillates (Covance Laboratories Inc 2000a)	OX15622 Undiluted (85% OGA 499)	25% OX15622 in mineral oil (21% OGA 499)	1st	*Test*	0	0	10	9	1	0	0	12	7	1	Sensitising
				Naïve	10	0	0	0	0	4	6	0	0	0	
			Total No. of test animals with positive response:				*20/20*					*20/20*			
		25% OX15622 in mineral oil (21% OGA 499)	2nd	*Test*	0	8	9	3	0	0	5	8	6	1	
				Naïve	2	5	3	0	0	2	7	1	0	0	
			Total No. of test animals with positive response:				*12/20*					*15/20*			
		2.5% OX15622 in mineral oil (2.1% OGA 499)	2nd	*Test*	17	3	0	0	0	15	4	1	0	0	
				Naïve	7	3	0	0	0	8	2	0	0	0	
			Total No. of test animals with positive response:				*0/20*					*1/20*			

TABLE 2 – INCIDENCE OF DERMAL RESPONSES FOLLOWING CHALLENGE (cont')

Test substance identity & formulation details	*Induction Concentration*	*Challenge Concentration*	*Challenge*	*Animal*	*Incidence of Dermal Responses*										*Result*
					24 hour					*48 hour*					
					0	*0.5*	*1*	*2*	*3*	*0*	*0.5*	*1*	*2*	*3*	
OX15623 75 wt% OGA 499 in Stoddard solvent & hydrotreated light distillates (Covance Laboratories Inc 2000b)	OX15623 Undiluted (75% OGA 499)	5% OX15623 in mineral oil (3.8% OGA 499)	1st	*Test*[1]	16	3	0	0	0	17	2	0	0	0	Non-Sensitising
				Naïve	10	0	0	0	0	8	2	0	0	0	
			Total No. of test animals with positive response:				*0/20*					*0/20*			
OX15624 50 wt% OGA 499 in Stoddard solvent & hydrotreated light distillates (Covance Laboratories Inc 2000c)	OX15624 Undiluted (50% OGA 499)	10% OX15624 in mineral oil (5% OGA 499)	*1st*	*Test*	15	5	0	0	0	14	6	0	0	0	Non-Sensitising
				Naive	10	0	0	0	0	8	2	0	0	0	
			Total No. of test animals with positive response:				*0/20*					*0/20*			
OGA 600 39% OGA 499 in Stoddard solvent, hydrotreated light distillates & 10% OGA 574 (Covance Laboratories Inc 1998b)	OGA 600 Undiluted (39% OGA 499)	OGA 600 Undiluted (39% OGA 499)	1st	*Test*	0	12	6	1	0	2	13	4	1	0	Non-Sensitising
				Naïve	0	9	1	0	0	0	9	1	0	0	
			Total No. of test animals with positive response:				7/20					5/20			
		OGA 600 Undiluted (39% OGA 499)	2nd	*Test*	2	16	2	0	0	4	15	1	0	0	
				Naïve	4	5	1	0	0	2	7	1	0	0	
			Total No. of test animals with positive response:				*2/20*					*1/20*			
		5% OGA 600 in mineral oil (2% OGA 499)	2nd	*Test*	20	0	0	0	0	18	2	0	0	0	
				Naïve	10	0	0	0	0	10	0	0	0	0	
			Total No. of test animals with positive response:				*0/20*					*0/20*			
OGA 600 Diluted to 1% OGA 499 in mineral oil. (Covance Laboratories Inc 1998a)	50% OGA 600 w/v in mineral oil (0.5% OGA 499)	25% OGA 600 w/v in mineral oil (0.25% OGA 499)	1st	*Test*	6	14	0	0	0	7	13	0	0	0	Non-Sensitising
				Naïve	1	9	0	0	0	1	9	0	0	0	
			Total No. of test animals with positive response:				*0/20*					*0/20*			

1 – One animal was euthanised on Day 29. Necropsy did not reveal treatment related effects.

9.1.6.5 Human Repeated Insult Patch Test (Hill Top Research Inc 1998)

Study Group:	152 females, 37 males (ages 21 to 60)
Test substance:	OGA 600, diluted with mineral oil to 0.2 wt% CP 2043 (OGA 499)
Induction procedure:	Nine repeat applications of the test substance (0.2 mL, 24 hour exposure, covered by a semi occlusive patch) at 3 applications/week for 3 weeks, to the same skin area of the deltoid region of the upper arm, followed by a 2-week rest period; Mineral oil served as the negative control and was administered similarly
Challenge procedure:	Same as induction procedure but applied to the other arm; challenge sites were examined for dermal reactions 48 and 96 hours post-application
Challenge outcome:	There were no reactions indicative of sensitisation to the test article or negative control following the challenge application
Test method:	OECD TG 40
Result:	OGA 600 (diluted to 0.2% wt OGA 499) was not considered a skin sensitiser in human volunteers.

9.2 Combined 4-Week Repeated Dose Oral Toxicity, Reproduction and Neurotoxicity Screen in Rats (WIL Research Laboratories Inc 1999)

The potential sub-chronic toxicity, neurotoxicity and reproductive toxicity related to the administration of the notified polymer were evaluated in a combined repeated dose study.

Investigated parameters common to all study phases included viability, clinical signs, bodyweight, food consumption and necropsy evaluations. Clinical pathology, organ weight and histopathology data (gross lesions only) were collected in the sub-chronic toxicity phase. Neuropathology, functional observational battery and motor activity data were collected in the neurotoxicity phase. Mating indices, neonatal parameters, organ weights and histopathology data were recorded in the reproduction phase.

Sub-Chronic Phase

Species/strain:	Rat/Crl:CD (SD)IGS BR
Number/sex of animals:	5/sex/group (control, treatment and recovery groups)
Method of administration:	Oral (gavage)
Dose/Study duration:	0, 100, 300 or 1 000 mg/kg/day for 28 consecutive days followed by a treatment free period of 16 days;
Test method:	OECD TG 407

Mortality:

One control group female was found dead on Day 4.

Clinical observations:
Clinical findings, bodyweight gain, food consumption were comparable to the control group throughout the treatment and recovery periods.

Clinical Pathology:

Serum Chemistry:
Significant findings at 1 000 mg/kg/day were increased mean globulin for males at the end of treatment (Week 4) and end of recovery (Week 6). Consequently, the Week 4 albumin/globulin ratio was reduced and the Week 6 total protein was increased. Increased mean aspartate aminotransferase (AST) and potassium in females at Week 4 were observed together with increased mean calcium at Week 6 in males.

Urinalysis:
No significant findings at Weeks 4 and 6.

Haematology:
Significantly increased neutrophil count (absolute and differential) and a decreased lymphocyte count (differential only) in males at 1 000 mg/kg/day at Week 4 and/or Week 6. However, the total leucocyte count for this group at Week 4 was comparable to that in the control group.
An increased incidence of anisocytosis was found in all treated females, and males of the 300 and 1000 mg/kg/day groups at Week 4, and in all treated animals at Week 6; the changes were considered minimal by the study authors. No changes in erythrocyte indices were observed.

Pathology:

Organ Weights:
Significantly increased mean spleen weights (absolute and relative to final body and brain weights) in the 1 000 mg/kg/day group females at the Week 4 necropsy. At the Week 6 necropsy, mean spleen weights relative to final body and/or brain weights for the 300 and 1 000 mg/kg/day group males were significantly increased relative to control group values.
Macroscopic:
No treatment related findings were observed.
Microscopic:
Gross lesions and other tissues examined at Week 4 and Week 6 did not reveal any treatment related effects.

Neurotoxicity Phase

Species/strain:	Rat/Crl:CD (SD)IGS BR
Number/sex of animals:	5/sex/group
Method of administration:	Oral (gavage)
Dose/Study duration:	0, 100, 300 or 1 000 mg/kg/day for 28 consecutive days
Test method:	OECD TG 407
Mortality:	Nil

Clinical observations:
No treatment related clinical findings. No remarkable differences in body weights or food consumption to that of controls.

Functional Observation Battery:
Home cage and Handling observations:
No remarkable differences were apparent between the control and treated groups.

Open field observations:
Significantly decreased mean time to first step for all treated female groups at the Week 4 evaluation.
Sensory observations:
Significantly increased number of males in the 300 mg/kg/day group with no reaction to the touch response test at the Week 2 evaluation, but not at the Week 4 evaluation or in animals of the 1 000 mg/kg/day group at any evaluation.
Neuromuscular observations:
Significantly increased hindleg grip strength mean for the 1 000 mg/kg/day group females at the Week 2 evaluation, but not at the Week 4 evaluation.
Physiological observations and motor activity:
No apparent effect on activity, catalepsy, body temperature or mean body weight between the control and treated groups.

Clinical Pathology:
Plasma cholinesterase:
Cholinesterase activity was comparable between the treated and the control group throughout the treatment and recovery periods.

Pathology:
Brain weight and dimensions:
No treatment related differences in mean brain weight or brain measurements.

Microscopy:
No remarkable neuropathological lesions in the control and 1 000 mg/kg/day groups.

Reproduction Phase

Species/strain:	rat/Crl:CD BR
Number/sex of animals:	12/sex/dose group
Method of administration:	Oral (gavage)
Doses:	0, 100, 300, or 1 000 mg/kg/day
Test method:	OECD TG 414

Dosing schedule:
Males were dosed for 28 consecutive days prior to mating, continuing for a total minimum dosing period of 71 or 72 days.
Females were dosed for 28 consecutive days prior to mating, continuing to the scheduled necropsy (lactation Day 4 for females that delivered a litter; post mating Day 25 for females that did not deliver a litter; 25 days after the termination of the breeding period for females with no evidence of mating).

F_0 generation findings:

Mortality:
One control female was found dead on lactation Day 4.

Reproductive performance:
Administration of test substance revealed no adverse effects in reproductive performance, or mating and fertility indices.

Gestation length and Lactation:
Differences between the treated groups and control were slight and were not statistically significant. No adverse signs were noted in the control or treated females during parturition.

Clinical observations:
Males of the 1 000 mg/kg/day group had increased incidence of yellow matting on the anogenital and urogenital areas during study weeks 7 through 11; dried red material around the nose and soft stool, generally between weeks 6 and 11.

Body weights:
Males of the 1 000 mg/kg/day group had significantly decreased mean body weights (13.5% relative to the control group at week 10), body weight gains and cumulative body weight gains which was attributable to administration of the test substance.

Pathology:
Organ weights -
In males of the 1 000 mg/kg/day group, mean absolute epididymal weights and mean liver weights (absolute and relative to brain weight) were significantly decreased compared to controls. The decrease was attributed to the reduced final body weight observed for this group. Mean brain, spleen, kidney and testis weights for males of the 1 000 mg/kg/day group were significantly elevated relative to final body weight. The mean testis weight relative to final body weight in the 300 mg/kg/day group was also significantly increased when compared to the control. However, the mean absolute weights for these organs were comparable to their respective control group values, as were the relative testes-to-brain weight values. The differences in organ-to-final body weight ratios were not considered to be related to treatment.
Macroscopy:
One female of the control group had no evidence of mating and was non gravid. One female of the 1 000 mg/kg/day group failed to deliver a litter. This female was non gravid. One female of the 100 mg/kg/day group had total litter loss on lactation Day 1. All 3 females were internally normal.
Microscopy:
No treatment related lesions were observed. The frequency of lesions observed in the 1 000 mg/kg/day group were similar to that observed for the control group, or the findings were noted for a limited number of animals.

F_1 generation findings

Litter data and postnatal survival:
No adverse effects on live litter size, viability, sex ratios or body weights or general physical condition at any dose level.

Mortality:
The number of pups examined that were found dead or euthanised *in extremis* were 16, 16, 10 and 3 in the control, 100, 300 and 1 000 mg/kg/day groups, respectively. In the same respective groups, 0, 3, 3 and 0 pups were missing and presumed to have been cannibalised.

Pup necropsies:
No significant treatment related findings.

Lactation Day 4:
Malformations - bilateral anophthalmia was observed in one pup of the 100 mg/kg/day group, and one pup of the 300 mg/kg/day group had hydrocephaly;
Developmental variations - one pup of the 1 000 mg/kg/day group had a major blood vessel variation; two pups of the control group and one pup of the 100 mg/kg/day group had a haemorrhagic ring around the iris; two pups of the control group had undeveloped renal papillae.

Conclusions:
There were no adverse effects on survival of the animals in the sub-chronic toxicity, neurotoxicity and reproduction phases. Increased incidence of yellow matting on the anogenital and urogenital areas, dried red material around the nose and soft stool were noted for the 1 000 mg/kg/day group males in the reproduction phase between study weeks 6 and 11. No treatment related clinical findings were observed at any dose level in the subchronic or neurotoxicity phases.

Treatment related decreased mean body weight (13.5% relative to the control group at week 10), body weight gains and cumulative body weight gain were observed in males of the 1 000 mg/kg/day group. These decreases were limited to the reproduction phase and were sustained from the second week of treatment until the end of the study. No similar changes were observed in the subchronic and neurotoxicity phases. Additionally no remarkable differences from the control group were observed for these parameters when the data from the subchronic, neurotoxicity and reproduction phases were combined for Weeks 0 to 4. Female weekly, gestational and lactational body weight and body weight gain were unaffected by test substance administration.

No test substance related changes in clinical chemistry or urine parameters were recorded during the subchronic toxicity phase. An increased incidence of anisocytosis was observed during the treatment and recovery phases in treated animals. However this finding occurred in the absence of other red blood cell changes.

No remarkable differences were found between the treated and control groups in the functional observational battery and motor activity evaluations. No treatment related neuropathological lesions were observed.

No adverse effects on reproduction in F_0 generation or development in the F_1 generation were observed.

Where examined, there were no treatment related macroscopic or microscopic lesions and no test substance related effects on organ weight data in adult male and female rats.

The No Observed Adverse Effect Level (NOAEL) determined for subchronic oral toxicity was 300 mg/kg/day, based upon substantial body weight decrease and clinical observations for the 1 000 mg/kg/day group males in the reproduction phase of the study. The NOAELs for neurotoxicity and reproductive toxicity were 1 000 mg/kg/day, based upon the absence of adverse neurotoxic, reproductive or developmental effects at this dose level.

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay (Safepharm Laboratories Limited 1998f)

Strains:	*Salmonella typhimurium* strains: TA 1535, TA 1537, TA 98, TA 100; *Escherichia coli* strain*:* WP2uvrA$^-$
Concentration range:	0, 15, 50, 150, 500, 1500 and 5000 μg/plate, each concentration was tested in triplicate, with or without metabolic activation, in two independent experiments; appropriate strain specific positive control reference substances were used
Metabolic activation system:	liver fraction (S9 mix) from rats pretreated with Aroclor 1254
Test method:	OECD TG 471 & 472 - plate incorporation method
Comment:	toxicity of the notified polymer was noted at 5 000 μg/plate for the strains TA100, TA 1535 and TA 1537 in the absence of S9 mix; an oily precipitate was noted at and above 1 500 μg/plate; there were no significant increases in revertant colony numbers at any dose level, in the presence or absence of metabolic activation; concurrent positive controls used in the test induced marked increases in the frequency of revertant colonies and the activity of the S9 fraction was found to be satisfactory
Result:	OGA499 was not considered mutagenic in the bacterial strains tested.

9.3.2. Chromosomal Aberration Assay in Chinese Hamster Lung Cells (Covance Laboratories Inc 1999b)

Cells:	Chinese Hamster Lung Fibroblasts
Metabolic activation system:	liver fraction (S9 mix) from rats pretreated with Aroclor 1254

Dosing schedule:	Each concentration was tested in duplicate, with or without metabolic activation (S9), in two independent experiments. The solvent was McCoy's 5a Culture Medium (ethanol and acetone were unsuitable);
	
	<u>Experiment 1:</u>
	without S9,
	0*, 100, 200, 400, 600*, 800, 1 000*, 1 200, 1 600 µg/mL;
	treatment/harvest time = 6/24 hours;
	positive control: 0.05µg/mL mitomycin C;
	
	with S9:
	0*, 0.310, 0.620, 1.24, two-fold dilutions to 314*, 626*, 1 250*, 2 500, 5 000 µg/mL,
	treatment/harvest time: 6/24 hours,
	positive control: 10µg/mL cyclophosphamide;
	
	<u>Experiment 2:</u>
	without metabolic activation,
	0*, 12.5, 25, 50*, 100*, 200*, 400, 600*, 800, 1 000, 1 200, 1 600 µg/mL;
	treatment/harvest time = 24/24 or 48/48 hours;
	positive control: 0.05µg/mL mitomycin C;
	
	with metabolic activation,
	0*, 200, 400, 600, 800, 1 000*, 1 200, 1 600*, 2 000*, 2 500 µg/mL,
	treatment/harvest time: 6/48 hours,
	positive control: 10µg/mL cyclophosphamide.
	
	asterisk* indicates cultures selected for metaphase analysis

Test method:	OECD TG 473

Comment:	At higher test concentrations toxicity was observed, generally without consistency between duplicate cultures. The difference in this observation was explained by the presence of precipitate at these concentrations inducing differential toxicity depending on its dispersion in the culture medium. 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:	OGA499 was not considered clastogenic under the conditions of the chromosomal aberration assay.

9.3.3 Micronucleus Assay in the Bone Marrow Cells of the Mouse (Safepharm Laboratories Limited 1998d)

Species/strain:	Mouse/Crl:CD-1 (ICR) BR
Number and sex of animals:	7 males/group
Doses/Method of administration:	test substance: 500 mg/kg (low), 1 000 mg/kg (mid) or 2 000 mg/kg (high); positive control: cyclophosphamide 50 mg/kg; vehicle control: arachis oil; vehicle control and test substance administered via intraperitoneal injection at a constant volume of 10 mL/kg bw; positive control was administered orally.
Sampling schedule:	Two sampling times: Vehicle control, positive control, low, mid and high dose animals sacrificed 24 hours after dosing; Vehicle control group and high dose animals sacrificed 48 hours after dosing;
Clinical observations:	no mortality; in the preliminary range finding study, clinical signs of toxicity were observed at 1 000 and 2 000 mg/kg during the 72 hour observation and included hunched posture, lethargy, piloerection and red/brown staining around the mouth

Micronuclei score:	no significant increase in micronucleated polychromatic erythrocytes (PCEs) caused by test substance at either sampling time; the ratio of PCEs to monochromatic erythrocytes (PCE/NCE) for each group was similar to the concurrent control group; the positive control caused a significant increase in micronucleated PCEs
Test method:	OECD TG 474
Result:	OGA 499 did not induce a significant increase in micronucleated PCEs in bone marrow cells of the mouse *in vivo.*

9.4 Overall Assessment of Toxicological Data

Toxicity Summary
The notified polymer, OGA 499, was of very low acute oral toxicity (LD_{50}>5 000 mg/kg) and low acute dermal toxicity (LD_{50}>2 000 mg/kg) in rats. It was a slight eye irritant and a slight to moderate skin irritant in rabbits. Although no acute inhalation studies have been conducted, the notified polymer is not expected to be an inhalation hazard based upon its low vapour pressure and high viscosity.

The skin sensitisation potential of OGA 499 and formulations that contain it has been investigated in guineapigs using the Buehler method. OGA 499 is a moderate to strong skin sensitiser in guineapigs. The nature of the skin sensitisation response for formulations containing OGA 499 varied with the composition of the formulation. A formulation containing OGA 499 at 85% in a mixture of Stoddard solvent & hydrotreated light distillates was also found to be sensitising to guineapig skin. However, formulations containing the same hydrocarbon mixture and OGA 499 at 75%, 50%, or 39% were not considered sensitising to guineapig skin. Formulations containing OGA 499 at 85% in light aromatic solvent naphtha, or OGA 499 at 1% in mineral oil were considered non-sensitising to guineapig skin. No interpretation of these findings was given by the notifier. The notified polymer did not elicit delayed contact hypersensitivity when tested at 0.2% in volunteers.

In a combined repeated oral dose study (sub-chronic toxicity, neurotoxicity and reproductive toxicity) rats received 0, 100, 300 or 1000 mg/kg/day of notified polymer. No treatment related findings were observed at any dose level in the subchronic or neurotoxicity phases. An increased incidence of yellow matting on the anogenital and urogenital areas, dried red material around the nose and soft stool were noted for males of the 1 000 mg/kg/day group in the reproductive study, in addition to a significant decrease in bodyweight in this group. These findings were considered to be treatment related. The No Observed Adverse Effect Level (NOAEL) determined for the subchronic oral toxicity was 300 mg/kg/day, based upon body weight effects and clinical observations for the 1 000 mg/kg/day group males in the reproduction phase of the study. The NOAELs for neurotoxicity and reproductive toxicity were 1 000 mg/kg/day based upon the absence of adverse neurotoxic, reproductive or developmental effects at this dose.

OGA 499 was not considered mutagenic in a bacterial reverse mutation assay. Genotoxicity was not observed in mammalian cells *in vivo* or *in vitro*.

Hazard Classification

The results of the acute oral and dermal studies in rats and the skin and eye irritant studies in rabbits are below the thresholds for health effects classification as hazardous for these endpoints under NOHSC (NOHSC 1999). In a non-adjuvant type test, the notified polymer, OGA 499 elicited a moderate to strong dermal sensitisation reaction in guineapigs. The sensitisation response for formulations containing OGA 499 appears to depend on the composition of the formulation. The 28-day repeat oral dose study did not reveal evidence of organ dysfunction or systemic toxicity, neurotoxicity or reproductive toxicity. The notified polymer was not considered mutagenic. Based upon the dermal sensitisation observed in guineapigs the notified polymer, OGA 499, meets the criteria for classification as a skin sensitiser under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 1999). Therefore, the overall hazard classification for the notified polymer is Irritant (Xi) with risk phrase R43- May Cause Sensitisation by Skin Contact.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The notifier has supplied ecotoxicity studies summarised in the following table. The tests were performed in compliance with OECD/EEC Test Methods (European Commission 1992), (OECD 1995-1996) and according to OECD Principles of Good Laboratory Practices.

10.1 Ecotoxicity Test Results

Test	***Species***	***Test concentrations (nominal) mg/L***	***Results (nominal) mg/L***
Acute Toxicity (Static Test) (OECD TG 203)	Rainbow trout *Oncorhynchus mykiss*	10, 18, 32, 56 & 100	96 h LC_{50} = 22 96 h NOEC = 10
Acute Toxicity - Immobilisation (Static Test) (OECD TG 202)	Water Flea (*Daphnia magna*)	1000	48 h EC_{50} > 1000 48 h NOEC = 1000
Growth Inhibition Growth (μ) & Biomass (b) (Static Test) (OECD TG 201)	Green Algae (*Pseudokirchneriella subcapitata*)	6.25, 12.5, 25, 50 & 100	$E\mu C_{50}$ = 11.0 E_bC_{50} = 8.8 NOEC = 6.25
Respiration Inhibition (OECD TG 209)	Activated Sludge - Aerobic Waste Water Bacteria	1000	3 h EC_{50} > 1000

10.1.1 Fish (Safepharm Laboratories Limited 1998h)

Rainbow trout were exposed to Water Accommodated Fractions (WAF) of the notified substance at nominal loading rates of 10, 18, 32, 56 and 100 mg/L for a period of 96 hours under semi-static test conditions. WAF were obtained by stirring the notified test material for 24 hours at each concentration followed by standing for 4 hours prior to removal of the aqueous phase. Based on these nominal loading rate WAF, the 96 hour LC_{50} was 22 mg/L with 95% confidence limits of 20 to 24 mg/L. The no observed effect concentration was 10 mg/L loading rate WAF. Sub-lethal effects of exposure were observed at and above the 18 mg/L loading rate WAF. Effects observed were swimming at the bottom, swimming at the surface, swimming at the bottom and hyperventilating, hyperventilating, loss of equilibrium and the presence of moribund fish. The concentration, homogeneity and stability of the test material in the test solutions were not determined.

10.1.2 Aquatic Invertebrates (Safepharm Laboratories Limited 1998g)

After 48 hours exposure of the notified polymer to *Daphnia magna* the EC_{50} was determined to be greater than a WAF of 1 000 mg/L. No immobilisation or other signs of intoxication were observed in *Daphnia magna* at that WAF concentration. WAF were made according to the method outlined above.

10.1.3 Algae (Safepharm Laboratories Limited 1998i)

After 96 hours exposure of the notified polymer to green algae *Pseudokirchneriella subcapitata* the $E\mu C_{50}$ was 11 mg/L and the E_bC_{50} was 8.8 mg/L. The no observed effect concentration at 96 hours was 6.25 mg/L WAF concentration. WAF were made according to the method outlined above.

10.1.4 Microorganisms (Safepharm Laboratories Limited 1998k)

The effect of the notified polymer on the respiration of activated sewage sludge microorganisms was studied. The test material (500 mg) was dispersed in approximately 250 mL of water and subjected to ultrasonication for 30 minutes. Synthetic sewage (16 mL), activated sewage sludge (200 mL) and water were added to give the test concentration of 1 000 mg/L. As a 3 hour EC_{50} of greater than 1 000 mg/L was observed, the no observed effect concentration was either greater than or equal to 1 000 mg/L.

10.2 Conclusion

The ecotoxicity data for the notified substance suggests that it has slight to moderate toxicity to fish and algae and is non-toxic to aquatic invertebrates and microorganisms. However, the studies on fish, daphnia and algae use WAF which could have much lower test substance concentrations, due to low water solubility, than the nominal ones provided. This is confirmed by Total Organic Carbon Analyses carried out by the notifier for the fish and daphnia studies. The results indicate that, on average, approximately 2 mg/L of the notified polymer is found within any given WAF regardless of the starting nominal concentration. The test substance is, therefore, likely to be at least moderately toxic to fish and algae. Acute toxic effects on aquatic invertebrates are not expected up to the limit of the notified polymers solubility.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The intended use pattern of the polymer in the fuel additive is not expected to result in a significant release to the environment. In the event of spills and minor releases during transfer operations, the MSDS of the additive package containing the polymer contains information on procedures to reduce release to the environment.

The notifier claims that the fuel additive will be completely destroyed by combustion within the petrol engine, resulting in oxides of carbon, nitrogen and hydrogen. Although there is no direct data to support this claim it is evident that the polymer, and other petrol constituents made up of hydrocarbon and oxygen will not survive the temperatures at which the fuel is exploded within the internal combustion engine.

Given the above, environmental exposure and the overall environmental hazard is expected to be low.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Based on the toxicological data submitted for OGA 499, the notified polymer is of very low acute oral toxicity and low acute dermal toxicity. It was a slight eye irritant and slight to moderate skin irritant in rabbits. The notifier claims that OGA 499 is not expected to be an inhalation hazard because the low vapour pressure (less than 1.33×10^{-3} kPa at 25°C) and high viscosity (275×10^{-6} m^2/sec at 40°C) would preclude aerosol formation under normal conditions.

The skin sensitisation potential of OGA 499 and formulations that contain it has been investigated in guineapigs using the Buehler method. OGA 499 is a moderate to strong skin sensitiser in guineapigs. The nature of the skin sensitisation response for formulations containing OGA 499 varies with the composition of the formulation. A formulation containing OGA 499 at 85% in a mixture of Stoddard solvent & hydrotreated light distillates was also found to be sensitising to guineapig skin. However, formulations containing the same hydrocarbon mixture and OGA 499 at 75%, 50%, or 39% were not considered sensitising to guineapig skin. Formulations containing OGA 499 at 85% in light aromatic solvent naphtha, or OGA 499 at 1% in mineral oil were considered non-sensitising to guineapig skin. The polymer did not elicit delayed contact hypersensitivity when tested at a challenge concentration of 0.2% in volunteers.

A 28-day repeat oral dose study did not reveal evidence of organ dysfunction or systemic toxicity, neurotoxicity or reproductive toxicity. The NOAEL determined for the subchronic oral toxicity was 300 mg/kg/day, based upon reduced body weight and treatment-related clinical observations for the 1 000 mg/kg/day group males in the reproduction phase of the study. The NOAELs determined for neurotoxicity and reproductive toxicity were 1 000 mg/kg/day based upon the absence of adverse neurotoxic, reproductive or developmental effects at this dose level. The notified polymer was not considered mutagenic, *in vivo* or *in vitro*. Based upon skin sensitisation observed in guineapigs the notified polymer meets the

criteria for classification as a skin sensitiser under the NOHSC *Approved Criteria for Classifying Hazardous Substances*. Therefore, the overall hazard classification for the notified polymer is Harmful (Xi) with risk phrase R43 – May Cause Sensitisation by Skin Contact.

Occupational Health and Safety
During importation and transport of additive packages containing OGA 499 in 8 000 L iso tanks, there is unlikely to be any worker exposure except in the event of a spill. Exposure after a spill would need to be controlled by use of the recommended practices for spillage clean up given in the MSDS supplied by the notifier. These workers will need to have access to protective clothing to minimise exposure.

The transfer and blending operations at the refinery/terminal facilities are enclosed and automatically operated. However, exposure to the additive package containing OGA 499 may occur during transfer operations as delivery lines are connected/disconnected from the import containers, and during sampling for laboratory analysis. The process in which the notified polymer is used is considered non-dispersive and exposure incidental. Inhalation will be a minor route of exposure given the high viscosity and low vapour pressure. Potential for slight, transient eye irritation may occur following eye contact. Skin contact is expected to be the major route of exposure; the health effect of concern by this route skin sensitisation.

The notifier expects OGA499 will be imported at up to 40% in additive packages, however, the exact concentration of OGA 499 and the composition details of the additive package are not known at this stage. On the basis of the variability in the skin sensitisation potential of formulations containing OGA 499 the risk of skin sensitisation cannot be excluded for OGA 499 in additive packages. Although the risk of skin sensitisation from OGA 499 is expected to diminish with the final blended petrol, containing less than 0.1% OGA 499.

Because of the hazardous nature of fuel and fuel products encountered at refineries and terminals standard operating procedures at these sites required workers to wear appropriate personal protective equipment to control exposure to these substances in order to minimise the risk of adverse health effects.

Only under the conditions described, that is enclosed automated systems and the mandatory use of appropriate personal protective equipment, is the risk of skin sensitisation for these workers considered minimal.

Fuel transporters, service station workers and mechanics will receive negligible exposure because of the very low concentration (maximum 0.1% w/w) of OGA 499 present in the final fuel. The risk of skin sensitisation for these workers is minimal.

Public Exposure
Dermal, inhalation, and possibly ocular exposure are likely to occur when filling petrol tanks at service stations. Consequently, public exposure would be occasional but widespread. Although the notified polymer is a slight to moderate skin irritant and a slight eye irritant, it is likely to be of minor hazard, based on its low concentration in petrol (maximum 0.1%) and its intermittent use. Minimal public exposure is expected during transport, blending with petrol and storage. It is considered that OGA 499 will not pose a significant hazard to public health when used in the proposed manner.

13. RECOMMENDATIONS

Occupational Health and Safety Matters
To minimise occupational exposure to OGA 499 the following guidelines and precautions should be observed:

- The notifier's MSDS be provided to the occupational health and safety officer during the workplace assessment process and to the authorised medical practitioner responsible for health surveillance in the workplace to alert them to the potential for skin sensitisation;

- Workers at refinery/terminal sites should receive regular instruction on good occupational hygiene practices in order to minimise personal contact, and contamination of the work environment with formulations that contain OGA 499. In particular, contaminated clothing should be removed without delay. The affected skin area should be decontaminated with a waterless hand cleaner, mineral oil, petroleum jelly, then washed with soap and water.

- Workers should be advised of the potential for occupational dermatoses following repeated skin exposure to OGA 499 and to report any skin changes to the occupational health and safety officer at their workplace. When an occupational skin disease occurs, work practices and opportunities for contact with the substance should be reviewed and preventive measures instigated 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).

- Personal protective equipment (PPE) should be used on all occasions where exposure to additive packages containing OGA 499 occurs. The notifier recommends Nitrile, Viton, polyurethane, or chlorinated polyethylene gloves. Chemical impervious clothing is also 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. Workers should be trained in the proper fit, correct use and maintenance of their protective gear. PPE guidance in the selection, personal fit and maintenance of personal protective equipment can be obtained from:

Protective eyewear:	AS 1336 (SAA 1994); AS/NZS 1337 (SAA/SNZ 1992).
Chemical impermeable clothing:	AS 3765.2 (SAA 1990).
Impermeable gloves:	AS 2161.2 (SAA/SNZ 1998).
Occupational footwear:	AS/NZS 2210 (SAA/SNZ 1994);

- Workplace practices and control procedures consistent with provisions of State, Territory and Commonwealth legislation based on the *National Model Regulations for the Control of Workplace Hazardous Substances* must be in operation if products containing OGA 499 are determined to be hazardous.

- OGA 499 is identified as a C2 combustible liquid and should be stored, handled and used in accordance with AS 1940 (SAA 1993);

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

Public Health Matters
If the conditions of use are varied, such as the concentration in petrol is increased, greater exposure of the public may occur. In such circumstances, secondary notification may be required to assess the hazards to public health.

14. MATERIAL SAFETY DATA SHEET

The MSDS for OGA 499 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

Under the Act, secondary notification of the notified polymer shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise.

Secondary notification may also be relevant when details of the proposed new Commonwealth fuel legislation have been clarified.

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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.
Diffuse beefy red	3 severe	Swelling with lids half-closed	3 mod.	Discharge with moistening of lids and hairs and considerable area around eye	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