File No: NA/641

December 1998

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Opalal

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

Opalal

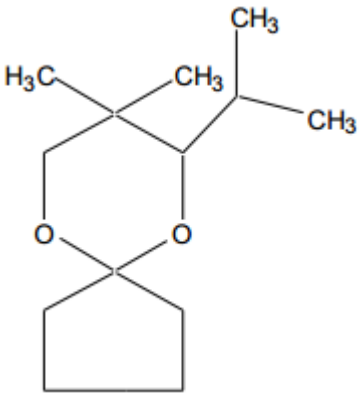
1. APPLICANT

Quest International Australia Pty Ltd of 6 Britton St, SMITHFIELD NSW 2164 has submitted a standard notification statement in support of their application for an assessment certificate for Opalal.

2. IDENTITY OF THE CHEMICAL

Chemical Name:	3,3-Dimethyl-4-isopropyl-1,5-dioxaspiro(4,5)decane
Chemical Abstracts Service (CAS) Registry No.:	62406-73-9
Other Names:	6,10-Dioxaspiro(4,5)decane,8,8-dimethyl-7-(1-methyl ethyl)
Trade Name:	Opalal
Molecular Formula:	$C_{13}H_{24}O_2$

Structural Formula:



Molecular Weight:	212

Method of Detection and Determination:	The notifier provided comprehensive spectroscopic data - infra red, UV/visible, NMR (^{1}H and ^{13}C) and mass spectroscopy - on the new chemical which may be used to identify the material. A Gas Liquid Chromatogram also accompanied the notification.
Spectral Data:	IR: no distinctive functional group peaks; strong peaks in the range 2850-2950 cm^{-1} and 900-1500 cm^{-1} only UV/Vis: no peaks in the range 200-900 nm ^{1}H nmr: 0.8 (singlet), 1.0 (complex), 1.1 (singlet), 1.7 (complex), 1.9 (complex), 3.1, 3.3, 3.5 (doublets) ppm ^{13}C nmr: 18.917, 19.329, 22.081, 22.621, 23.215, 24.193, 29.241, 30.539, 34.014, 39.903, 74.650, 83.373, 110.403 ppm mass spectrum: m/e 212 (m^{+}), 197, 183, 169, 157, 140, 129, 127, 113, 111, 97, 85, 83, 69, 67, 56, 55, 43, 41

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	clear colourless liquid
Boiling Point:	233°C
Specific Gravity:	0.949 at 21°C
Vapour Pressure:	9.5_10^{-3} kPa at 20°C 1.4_10^{-2} kPa at 25°C
Water Solubility:	63.5 mg/L at 25°C
Partition Co-efficient (n-octanol/water):	log K_{ow} = 5.33
Hydrolysis as a Function of pH:	$T_{1/2}$ < 1 day at pH 4.0 $T_{1/2}$ = 208 days at pH 7.0 $T_{1/2}$ > 1 year at pH 9.0
Adsorption/Desorption:	log K_{oc} = 2.49-2.71
Dissociation Constant:	no acidic or basic functional groups
Flash Point:	97°C

Flammability Limits:	not determined
Autoignition Temperature:	approximately 384°C
Explosive Properties:	not expected to be explosive
Reactivity/Stability:	not expected to be reactive

Comments on Physico-Chemical Properties

The notified chemical is a high boiling point organic liquid with no highly polar or reactive functional groups. The vapour pressure is sufficiently low that it will not provide an unusual flammability hazard except when heated.

It is evident from the proposed use of Opalal that it will most readily be identified by smell.

Water solubility was determined by stirring an excess of the test substance with 100 mL of distilled water at 30ºC, equilibrating for at least 24 hours at 20°C, then separating the aqueous and non aqueous layers by centrifugation. The content of the new chemical in the aqueous phase was then determined by gas chromatography. The average of three separate determinations gave the water solubility as 63.5± 2.2 mg/L at 20°C.

The Henry's law constant was calculated from the molecular weight, the measured water solubility and vapour pressure through the equation:

H= MW(g/mole) × Vapour Pressure (Pa)/Water solubility (g/L).

The compound contains an acetal linkage which is susceptible to hydrolysis under acidic conditions, and more slowly under neutral conditions. The rate of hydrolytic degradation of aqueous solutions containing measured concentrations of the test material (26.5-27.6 mg/L) was determined in duplicate at pH 4, 7 and 9 at 50°C over test periods of up to 10 days. Samples were analysed for the undegraded Opalal at least twice after commencement of the tests (2.4 h and 6 h at pH 4; 48, 120 and 288 h at pH 7; 48 h and 120 h at pH 9) by extraction of organic material from the aqueous liquid with chloroform, and determination using gas chromatography. A second study at pH 7 at temperatures of 50, 60 and 70°C was used to better define the temperature dependence of hydrolysis at this pH, and provided the value for $t_{1/2}$ at 25°C of 208 days.

This data is interpreted to indicate a half life of less than 1 day under acid conditions (pH 4) to greater than 208 days at 25°C at pH 9.

The n-octanol/water partition coefficient was determined using the HPLC method (European Economic Community, 1992). In this method the retention time of the test compound on C_{18} columns is compared with those of eight reference compounds with known values for Log

K_{ow} ranging from 1.1 (benzyl alcohol) to 6.2 (DDT). The determined value of Log K_{ow} = 5.33 indicates the new chemical has a high affinity for hydrocarbon-like environments.

The value of Log K_{oc} was determined using the method of the OECD draft guideline: Screening Method for the Determination the Adsorption Coefficient on Soil using High Performance Liquid Chromatography. In this method the retention time of the test compound on specially prepared columns is compared with those of eight reference compounds with known values for Log K_{oc} ranging from 1.81(atrazine) to 4.34 (pentachloronitrobenzene). The determined value of Log K_{oc} being close to 2.6 indicates the new chemical has only moderate affinity for the organic component of soils, and would not be strongly associated with these materials.

The compound contains no functionalities capable of dissociating or otherwise becoming ionised in aqueous media, and the notifier indicates that dissociation constant data are not applicable.

The surface tension of an aqueous solution containing approximately 46.7 mg/L (73% saturation) of the test substance was 64.6 mN/m at 20±0.5°C (water = 72.2 mN/m), indicating the material is not surface active.

Calculations based on the molecular structure using the quantitative structure activity relationships (QSARs) of the US Environment Protection Agency ASTER database (US Environment Protection Authority, 1998) furnished the following estimates for environmentally relevant physico-chemical parameters. Comparison with the data supplied by the notifier is not good, except for the water solubility.

ASTER data (all calculated using QSAR's)

Property	**QSAR estimate**
Boiling Point:	256 °C
Vapour Pressure:	0.449 Pa
Water Solubility:	65.3 mg/L
Henry's Law Constant:	1.44 $Pa/m^3/mole$
Log Kow:	3.50
Log Koc:	3.24
Hydrolysis:	Hydrolytic degradation unlikely.

4. PURITY OF THE CHEMICAL

Degree of Purity:	>99 %
Toxic or Hazardous Impurities:	none
Non-hazardous Impurities (> 1% by weight):	none
Additives/Adjuvants:	the notified chemical will be imported as a component, 0.1 % to 25 %, of a number of compounded fragrances; the identity of the other components of the compounded fragrances has not been disclosed

5. USE, VOLUME AND FORMULATION

The notified chemical will be used as an aroma chemical and will be blended with other such chemicals to produce compounded fragrances for products such as soaps, detergents and air fresheners. The notified chemical will comprise 0.1 % to 25 % of the compounded fragrances, with a typical level being around 5 %. The end use products will reportedly commonly contain 1-2 % of the fragrance mixture, therefore a maximum of 0.5 % of the notified chemical. This maximum concentration is only likely to be approached in solid air fresheners.

The compounded fragrances will not be manufactured in Australia. The import volumes are estimated to be 250 kg per annum in the first 3 years, possibly reaching 500 kg per annum after this time. The import volumes are estimates for the volume of notified chemical in the imported fragrance mixtures.

6. OCCUPATIONAL EXPOSURE

The compounded fragrances will be imported in 200 L polythene or lacquer lined steel drums. No exposure of the compounded fragrances containing the notified chemical to waterside, transport or warehouse workers is expected except in the case of an accident involving spillage.

The notified chemical is likely to be used as a component of the fragrance for a wide variety of products for household use. The fragrances will be blended into the consumer products by a number of customers using a variety of mixing techniques. It is estimated that between 5 and 20 process workers will be exposed to the notified chemical at each production line where it is used.

The notifier has provided a description of the type of operation which will be carried out in the production of several types of product containing the notified chemical. The examples

given are for production of air fresheners, soap bars and liquid soaps. The fragrance mixture used in soap manufacture is expected to include a maximum of 2 % notified chemical; while the fragrance mixture used in air fresheners will contain up to 25 % notified chemical.

All processes described will be carried out in closed systems, and therefore worker exposure is most probable at the time when new drums of fragrance mixture are being connected to the production system, and in the cleaning of milling and blending equipment. The most probable routes of exposure are inhalation and dermal exposure to drips and spills.

The notifier indicates that adequate ventilation should be provided in the customer facilities, including local exhaust ventilation during filling operations, and that gloves should be worn during procedures involving a risk of dermal exposure. Overalls, safety goggles and respiratory protection should be used where appropriate.

Exposure to the products containing the fragrances during packaging operations should present a low hazard as this is the form which will be provided for sale to the general public.

7. PUBLIC EXPOSURE

As the notified chemical will be used in a wide range of household products (soaps, detergents and air fresheners containing compounded fragrances) there will be widespread public exposure. Routes of exposure will include inhalation (of air fresheners), ocular, and systemic absorption across the skin (due to the molecular weight of 212 Daltons), which is likely to be the main route of exposure.

Exposure of the general public to the concentrates of the compounded fragrances is unlikely as these products are only used within an industrial environment.

8. ENVIRONMENTAL EXPOSURE

Release

The notifier indicated that production activities involving use of the new chemical would be performed by a number of different companies at a number of sites, and it is expected that production activities will take place in purpose constructed facilities.

The notifier indicates that around 1 % of the new chemical (annually 5 kg) may be lost as a consequence of cleaning the blending and filling equipment, and this would be discharged to the sewer system. No reference to the quantities of chemical likely to be lost and released as a result of accidental spillage was made in the submission. However, it is reasonable to estimate that a further 1 % of total import quantity could be lost through accident, which amounts to an annual release of another 5 kg.

The empty steel and polythene drums of fragrance will be washed and reused. No estimates

of the amount of residual chemical left in the drums was presented in the application, but a reasonable estimate is that this could amount to 0.05 - 0.1 % of the import quantity, or around 250-500 g per annum, and it is probable that this would also be washed into the sewer.

Consequently it is estimated that annually around 10-11 kg of the imported chemical could be discharged directly to the sewerage system.

However, the new chemical is a fragrance for use in domestic cleaning and personal care products, and consequently all will be eventually released into the environment as a result of normal product usage. It is expected that this release would be primarily to the sewage system, although due to the reasonably high vapour pressure much would be expected to volatilise and enter the atmosphere.
Empty containers of the consumer products are likely to contain some residual unused product, and these packages would be discarded with domestic garbage and be disposed of into landfill.

Fate

- **Biodegradation**

The notifier provided a laboratory report on the assessment of the biodegradation of Opalal conducted in accordance with the OECD Test Guideline TG 301F (Manometric Respirometry Test) (Organisation for Economic Cooperation and Development, 1992c). The results of this test (performed in triplicate) indicated approximately 2 % loss of initial Chemical Oxygen Demand (COD) of the test material after 28 days, and accordingly the Opalal cannot be classed as either readily biodegradable or as inherently biodegradable.

- **Models**

All the new chemical will eventually be released into the environment, and the majority could be expected to be discharged into sewerage systems. However, once released in this manner the relatively high vapour pressure indicates significant partitioning into the atmospheric compartment. For that proportion of the chemical which reaches sewage treatment plants (i.e. is not volatilised or otherwise destroyed during passage to the plant), the notifier presented the results of calculations from the SimpleTreat Model (European Commission, 1996). These estimates were based on the chemical having a calculated Henry's constant of 46.7 $Pa/m^3/mole$, a Log K_{ow} = 5.33 and being not biodegradable, and indicated that the chemical would be expected to partition into the air, water and sewer sludge compartments as follows

Air	Water	Sewer Plant Sludge
6%	12%	82%

Mackay Level 1 calculations from the ASTER database (US Environment Protection Authority, 1998) indicate that the chemical would partition primarily to the atmosphere. The

Mackay model assumes an equilibrium is established between all phases. In the environment an equilibrium state will not be reached as chemical which reaches the atmosphere will be effectively removed from the system by diffusion and destruction through reaction with hydroxyl radicals - see further below. The partitioning into the various environmental compartments resulting from this model is:

Atmospheric compartment	25.43%
Soil compartment	12.54%
Sediment compartment	11.71%
Water compartment	50.30%
Aquatic biota compartment	0.01%

Considering the assumptions and approximations inherent in both these estimation models, the differences between the two sets of results cannot be considered surprising or contradictory, and the differences can be primarily attributed to the difference between the measured value of Log K_{ow} (i.e. 5.33) and that calculated by QSAR (3.50). Both methodologies indicate partitioning to the atmosphere, and while the Mackay calculations indicate more partitioning to this compartment, it should be appreciated that as the compound is destroyed in the atmosphere through reaction with hydroxyl radicals (see below), it would be replenished from that in the water in order to maintain the equilibrium distribution.

- **Atmosphere**

Once released to the atmosphere it is considered that the chemical would be quickly decomposed through photolytically promoted free radical reactions. Hence, over time the sediment/water and water/air partitioning will be driven toward the loss of the chemical to the atmosphere. In the atmosphere it is likely that the substance will be degraded through reaction with hydroxyl radicals (through hydrogen abstraction mechanisms), and a calculation (Organisation for Economic Cooperation and Development, 1992d) indicates that in the troposphere the new chemical would react in this manner with a rate constant estimated as 32.1×10^{-12} cm^3/molecule/s. Rate constants of this order are indicative of rapid degradation (Organisation for Economic Cooperation and Development, 1992d), and the compound is not expected to persist in the atmosphere.

- **Sediment**

The new chemical is hydrophobic in character with Log K_{ow} = 5.33 and Log K_{oc} = 2.6; consequently when released into the sewer system some may remain associated with the organic component of the particulate matter present in the raw sewage, and eventually become incorporated into sediments. Here it would be slowly degraded through biological and abiotic processes to water, carbon dioxide and methane.

- **Soil**

Residual chemical disposed of to landfill via empty drums, discarded consumer packaging or within residual solids derived from water treatment at the production facilities, would also be expected to volatilise and enter the atmosphere. However, some chemical may remain adsorbed to soil particles, and in this situation would be expected to be slowly destroyed by similar mechanisms to those operating in sediments. Any waste material containing the notified chemical placed into compost facilities could also be expected to be destroyed through aerobic and anaerobic biological degradation processes. Incineration of the material would produce water vapour and oxides of carbon.

- **Bioaccumulation**

The ASTER calculations (US Environment Protection Authority, 1998) also provide an estimate of 231 for the bioaccumulation factor for the compound in fish (fathead minnow), indicating the compound has some potential for bioaccumulation. While reasonably soluble, the compound is also volatile and is therefore not expected to have prolonged residence times in the aquatic compartment.

9. EVALUATION OF TOXICOLOGICAL DATA

All toxicity testing was conducted using Opalal.

9.1 Acute Toxicity

Summary of the acute toxicity of Opalal

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} > 2000 mg/kg	(McRae, 1996b)
acute dermal toxicity	rat	LD_{50} > 2000 mg/kg	(McRae, 1996a)
skin irritation	rabbit	moderate irritant	(Parcell, 1996b)
eye irritation	rabbit	slight irritant	(Parcell, 1996a)
skin sensitisation	guinea pig	non-sensitising	(Selbie, 1996)

9.1.1 Oral Toxicity (McRae, 1996b)

Species/strain: rat/Hsd/Ola:Sprague-Dawley(CD)

Number/sex of animals: 5/sex

Observation period: 15 days

Method of administration: gavage, test material used as supplied; dose 2000 mg/kg

Clinical observations:	no deaths occurred during the study
Mortality:	piloerection was observed in all animals within 5 minutes of dosing; in 4 males and 4 females this was accompanied by increased salivation; the piloerection persisted for two days while the increased salivation was only observed on day 1
Morphological findings:	no macroscopic findings were observed at necropsy
Test method:	limit test, OECD TG 401 (Organisation for Economic Cooperation and Development, 1987c)
LD_{50}:	greater than 2000 mg/kg
Result:	the notified chemical was of very low acute oral toxicity in rats

9.1.2 Dermal Toxicity (McRae, 1996a)

Species/strain:	rat/Sprague Dawley(Crl:CD BR VAF PLUS)
Number/sex of animals:	5/sex
Observation period:	15 days
Method of administration:	semi-occluded patch; 24 hour exposure; at the end of this time excess test material was removed with warm water and paper towel dose 2000 mg/kg; test material used as supplied
Mortality:	no deaths occurred during the study
Clinical observations:	no clinical signs of toxicity were observed during the study
Morphological findings:	no macroscopic findings were observed at necropsy
Test method:	limit test, OECD TG 402 (Organisation for Economic Cooperation and Development, 1987a)
LD_{50}:	greater than 2000 mg/kg
Result:	the notified chemical was of low dermal toxicity in rats

9.1.4 Skin Irritation (Parcell, 1996b)

Species/strain: rabbit/New Zealand White

Number/sex of animals: 3 male

Observation period: 14 days

Method of administration: 0.5 mL of test material was applied to a clipped intact region of the dorsal skin and secured under a gauze patch with a semi-occlusive dressing for 4 hours; at the end of this time residual material was removed with lukewarm water and paper towel; animals were examined for skin reaction 1, 24, 48 and 72 hours following application of the test substance; additional observations were made on days 5 to 14

Draize scores (Draize, 1959) :

Time after treatment (days)	***Animal #***		
	1	***2***	***3***
Erythema			
1	[2a]	2	2
2	2	2	1
3	2	2	1
Oedema			
1	2	1	1
2	2	1	0
3	2	1	0

[a] see Attachment 1 for Draize scales

Observations: very slight to well defined erythema was observed for all animals for the entire 14 days of observation; very slight to moderate oedema for all animals, visible for 1 day for one animal, for 12 days for another and throughout the study for the third animal; cutaneous dryness and sloughing in all animals evident from day 7 or 8 through to the termination of the study

Test method: OECD TG 404 (Organisation for Economic Cooperation and Development, 1992a)

Result: the notified chemical was moderately irritating to the skin of rabbits

9.1.5 Eye Irritation (Parcell, 1996a)

Species/strain: rabbit/New Zealand White

Number/sex of animals: 3 male

Observation period: 7 days

Method of administration: 0.1 mL of test material applied as supplied into lower everted lid of one eye of each animal; the contralateral eye served as the control; animals were examined for eye lesions 1, 24, 48 and 72 hours after test substance application with further observations after 4 and 7 days

Draize scores (Draize, 1959) of unirrigated eyes:

	Time after instillation									
Animal	***1 day***		***2 days***		***3 days***		***4 days***		***7 days***	
Cornea										
1	0[1]		0		0		0		0	
2	0		0		0		0		0	
3	0		0		0		0		0	
Iris										
1	0		0		0		0		0	
2	0		0		0		0		0	
3	0		0		0		0		0	
Conjunctiva	***r***	***c***	***r***	***c***	***r***	***c***	***r***	***c***	***r***	***c***
1	2	1	1	1	1	1	0	0	0	0
2	1	1	0	0	0	0	0	0	0	0
3	2	1	2	1	2	1	1	1	0	0

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

Test method: OECD TG 405 (Organisation for Economic Cooperation and Development, 1987b)

Observations; diffuse crimson colouration of the conjunctiva one hour after installation for all animals; this persisted

	for up to 4 days; considerable swelling and partial eversion of the eyelid in one animal; chemosis lasted for up to 4 days no corneal or iridal inflammation was observed
Result:	the notified chemical was slightly irritating to the eyes of rabbits

9.1.6 Skin Sensitisation (Selbie, 1996)

Species/strain:	guinea pig/Dunkin Hartley
Number of animals:	test group 10/sex control group 5/sex

Induction procedure:

test group:

day 1:	to a clipped area of the scapular dorsal skin, each animal received 3 pairs of 0.1 mL injections as follows – • 1:1 (v/v) mixture of Freund's Complete Adjuvant and 0.9 % (w/v) physiological saline • the test material diluted to 1 % in corn oil • the test material diluted to 2 % in corn oil, mixed 1:1 (v/v) with Freund's Complete Adjuvant; final test material concentration 1 %
day 7	the same skin area was clipped and shaved and a filter paper patch saturated with 100 % test material was held in place under a polythene patch for 48 hours

control group:

day 1:	to a clipped area of the scapular dorsal skin, each animal received 3 pairs of 0.1 mL injections as follows –

- 1:1 (v/v) mixture of Freund's Complete Adjuvant and 0.9 % (w/v) physiological saline
- corn oil
- corn oil, mixed 1:1 (v/v) with Freund's Complete Adjuvant

day 7 as for test group but with a plain filter paper patch

Challenge procedure:

day 20 a filter paper patch soaked in a 5 % solution of test material in acetone/PEG 400 was applied to both test and control animals; the patch was covered with an aluminium patch test cup and held in place for 24 hours; the animals were examined for skin reactions 24 and 48 hours after removal of the patches

Challenge outcome:

	Test animals		***Control animals***	
Challenge concentration	***24 hours****	***48 hours****	***24 hours***	***48 hours***
5%	**0/20	0/20	0/10	0/10

* time after patch removal
** number of animals exhibiting positive response

Test method: OECD TG 406 (Organisation for Economic Cooperation and Development, 1992e)

Result: the notified chemical was not sensitising to the skin of guinea pigs

9.2 Repeated Dose Toxicity (Allan, 1996)

Species/strain: rat/Sprague Dawley(Crl:CD BR VAF PLUS)

Number/sex of animals:
group 1: 10/sex
group 2: 5/sex
group 3: 5/sex
group 4: 10/sex

Method of administration: gavage, 5 mL/kg/day test substance in corn oil, 0, 3, 30, 100 mg/mL

Dose/Study duration::	group 1: 0 mg/kg/day group 2: 15 mg/kg/day (low dose) group 3: 150 mg/kg/day (intermediate dose) group 4: 500 mg/kg/day (high dose) the study duration was 28 days; 5 animals per sex in groups 1 and 4 were then allowed to recover for 28 treatment free days
Clinical observations:	no clinical signs of toxicological importance in any of the animals; increased salivation, wet fur and subsequent fur loss and paddling of the forepaws following dosing were stated to be related to the unpalatability of the test substance and discomfort following dosing bodyweight gains in all treated females were lower than controls; the effect was found in the 500 mg/kg/day group throughout the treatment period and for the 150 and 15 mg/kg/day groups, for the last two weeks of treatment; it was not seen in males
Haematology	packed cell volume, haemoglobin concentration and red blood cell counts lower than control for 500 mg/kg/day females after treatment period; mean corpuscular volume slightly higher than control for the same group; reticulocyte counts statistically significantly higher than control for 500 mg/kg/day males and females and 150 mg/kg/day males after treatment period marginally higher than control mean corpuscular haemoglobin concentration for 150 and 500 mg/kg/day males and higher than control levels of neutrophils for 15, 150 and 500 mg/kg/day males and levels of monocytes for 500 mg/kg/day males were considered incidental after 28 days recovery, higher than control reticulocyte levels and lower than control packed cell volume, haemoglobin concentration and mean corpuscular haemoglobin concentration were observed for treated males; no other differences were observed

Clinical chemistry		after the treatment period, blood triglyceride and cholesterol levels were higher than the controls for 150 and 500 mg/kg/day males and cholesterol levels were also high for 500 mg/kg/day females; glucose levels were lower than the controls for 500 mg/kg/day males and females; alkaline phosphatase levels were lower than the controls for 500 mg/kg/day females; albumin levels for 500 mg/kg/day females and globulin levels for 500 mg/kg/day males and females (and thus total protein levels) were statistically significantly higher than the controls
		statistically significant decreases in chloride levels were observed for 500 mg/kg/day males and females but the individual levels were all within the historical range
		no biochemical differences from the controls were observed at the end of the recovery period
Gross pathology:		no macroscopic changes were observed at the end of the treatment phase or the recovery period
Organ weights		
	liver:	relative liver weights for 500 mg/kg/day males and females were higher than the controls
	kidney:	relative kidney weights for 500 mg/kg/day males and females were higher than the controls but in the absence of histopathological findings the study authors did not consider this treatment related
	spleen:	relative spleen weights for 500 mg/kg/day females were statistically significantly higher than the controls
	other:	no other statistically significant differences from controls were observed
	recovery period:	the relative liver weights for 500 mg/kg/day males were higher than the controls after the recovery period; the right epididymis weight for 500 mg/kg/day males was lower than the controls although this was not considered treatment related

Histopathology:

liver:	centrilobular hepatocyte hypertrophy was seen in the liver of all males and three females treated at 500 mg/kg/day and one male at 150 mg/kg/day (minimal to trace)
kidney:	an increase in incidence and degree of eosinophilic inclusions was seen in the kidneys of the 150 and 500 mg/kg/day males
spleen:	dose related incidence of haemosiderosis was seen in the spleen of all 500 mg/kg/day females (minimal), two of the 150 mg/kg/day females (trace) and one of the 15 mg/kg/day females; the finding of haemosiderosis in the low dose animal was considered unlikely to be related to the treatment by the study authors
other:	follicular epithelial hypertrophy (minimal) was seen in the thyroid of males and females treated at 150 and 500 mg/kg/day
recovery period	after the recovery period no significant histopathological differences between the treated group and the controls were observed
Test method:	OECD TG 407 (Organisation for Economic Cooperation and Development, 1995)
Result:	the authors established a NOAEL of 15 mg/kg/day, based on the dose related incidence of haemosiderosis seen in the spleen of female rats at 150 and 500 mg/kg/day; a NOEL could not be established because treatment related effects on bodyweight gain were found in female rats at all doses

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* Reverse Mutation Assay (Windebank, 1996)

Strains:	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537
Concentration range:	5000, 1500, 500, 150, 50, 15 and 5 µg/plate (all strains, with metabolic activation) 5000, 1500, 500, 150, 50 and 15 µg/plate (TA1535, without metabolic activation) 1500, 500, 150, 50, 15, 5, 1.5 and 0.5 µg/plate (TA100 and TA98, without metabolic activation) 500, 150, 50, 15, 5, 1.5 and 0.5 µg/plate (TA1537, without metabolic activation)
Metabolic Activation System:	rat liver S9 fraction from animals pretreated with Arochlor 1254
Test method:	OECD TG 471 (Organisation for Economic Cooperation and Development, 1983b)
Positive controls	2-aminoanthracene 2 µg/plate – TA1535, TA1537 with metabolic activation 2-aminoanthracene 1 µg/plate – TA100, TA98 with metabolic activation sodium azide 2 µg/plate – TA1535, TA100, without metabolic activation 2-nitrofluorene 1 µg/plate – TA 98 without metabolic activation 9-aminoacridine 20 µg/plate – TA 1537 without metabolic activation
Comment:	in the presence of metabolic activation, toxicity was observed for all strains at 500 µg/plate; in the absence of metabolic activation, all strains except TA1535 showed toxicity at 50 µg/plate; for TA1535, toxicity was observed at 5000 µg/plate no substantial increase in the number of revertant colonies or indication of clear dose response was observed in any test the positive controls produced clear positive results indicating that the test system responded appropriately

Result:	the notified chemical was not mutagenic in the bacterial strains tested in the absence or presence of metabolic activation provided by rat liver S9 fraction

9.3.2 Chromosomal Aberrations in Human Lymphocytes *In Vitro* (Ackhurst, 1996)

Cells:	human lymphocytes treated with phytohaemag-glutinin
Doses:	test material 25-200 µg/mL (without metabolic activation) 50-250 µg/mL (with metabolic activation) positive controls mitomycin C 0.2-0.8 µg/mL (without metabolic activation) cyclophosphamide 15-25 µg/mL (with metabolic activation)
Metabolic Activation System:	rat liver S9 fraction from animals pretreated with Arochlor 1254
Test method:	OECD TG 473 (Organisation for Economic Cooperation and Development, 1983a)
Treatment Regime:	with metabolic activation: test material (in ethanol) or positive control added to cell cultures in medium, with 250 µL/mL S9 mix, for 3 hours; the cells were then washed and cultured in fresh medium for a total time of 21 or 45 hours without metabolic activation: test material (in ethanol) or positive control added to cell cultures in medium and incubated for a total of 21 or 45 hours without a change of medium colcemid was added to all cultures 2 hours before harvest to arrest cells in metaphase
Observations:	toxic effects were observed between 100 and 200 µg/mL in the different studies; up to the highest

	doses used no statistically significant increase in the proportion of aberrant cells was seen compared with the solvent controls either in the presence or absence of metabolic activation
	statistically significant increases in cells showing structural chromosome aberrations occurred for the positive control substances, indicating that the test system responded appropriately
Results:	the notified substance did not induce structural chromosome aberrations in the presence or absence of metabolic activation

9.4 Overall Assessment of Toxicological Data

The acute oral toxicity in rats is very low (LD_{50}>2000 mg/kg) and the acute dermal toxicity in rats is low (LD_{50}>2000 mg/kg).

The notified chemical is a moderate irritant to rabbit skin, producing erythema which persisted for at least 14 days and oedema which persisted for up to 12 days. Opalal is determined to be a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (Approved Criteria) (National Occupational Health and Safety Commission, 1994a), because of (1) the erythema score over the first 72 hours of the test and (2) the persistence of skin irritation over the 14 days of the study. Opalal is classified as irritant and warrants the risk phrase R38, 'Irritating to the skin'.

The notified chemical did not elicit corneal or iris effects in rabbit eyes. Conjunctival redness and chemosis both persisted for up to four days after application of the test material and therefore Opalal must be considered to be a slight eye irritant. The mean scores for conjunctival effects were below the threshold for classification as irritating to eyes according to the Approved Criteria.

The notified chemical was not found to be a skin sensitiser in guinea pigs in an adjuvant skin sensitisation study.

In a 28 day repeat dose oral toxicity study in rats, the animals were administered the notified chemical by gavage at 0, 15, 150 or 500 mg/kg/day. The most significant findings related to the liver and spleen of the treated animals when compared to controls. Treatment related effects in the liver included increased liver weight plus centrilobular hepatocyte hypertrophy. The study authors suggested that these effects, plus the biochemical findings, reflected an adaptive change in the liver. Treatment related effects in the spleen included an increase in spleen weight accompanied by haemosiderosis (considered an adverse effect in the high and intermediate dose groups). This was possibly related to haemolysed red blood cells, as

evidenced also by effects on red blood cell parameters in high dose females, and high reticulocyte counts for high dose males and females.

Increased kidney weight accompanied by histopathological changes were observed in the kidneys of male rats; however the study authors suggested this was indicative of light hydrocarbon nephropathy syndrome (Alden, 1986) and that this is not considered predictive of a similar effect in man (Halder, 1984; Hard, 1993). The effects were only partially reversible. Treatment related thyroid hypertrophy was also observed in the high and intermediate dose groups.

A NOEL could not be established because of the effects on bodyweight gain found at all doses. The observed effects of treatment were found to be reversible after a 28 day recovery period.

The notified chemical was not mutagenic in bacterial test systems nor did it induce chromosomal aberrations in an *in vitro* human lymphocyte cytogenetic assay.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The notifier provided the following ecotoxicity data in support of their application. The ecotoxicity tests were performed in accordance with OECD Test Guidelines 203 (Organisation for Economic Cooperation and Development, 1992b), 202 (Organisation for Economic Cooperation and Development, 1984c), 201 (Organisation for Economic Cooperation and Development, 1984b) and 209 (Organisation for Economic Cooperation and Development, 1984a).

Test	***Species***	***Results***	***Reference***
acute toxicity	*Brachydanio rerio* (zebra fish)	LC_{50} (96 h) = 11.27 mg/L 0.98 < NOEC(96 h) < 2.26 mg/L	(Vaughan, 1996)
acute immobilisation	*Daphnia magna*	EC_{50} (48 h) > 11 mg/L NOEC (48 h) = 3.4 mg/L	(Flanagan, 1996)
algal growth inhibition	*Scenedesmus subspicatus*	EbC_{50} (72 h) = 8.2 mg/L NOEC (72 h) = 3.6 mg/L	(Roebuck, 1996)
inhibition of bacterial respiration	sewage sludge bacteria	Eb_{50} (3 h) > 1,000 mg/L NOEC(3 h) > 100 mg/L	(Mead, 1997)

* NOEC - no observable effect concentration

The tests on zebra fish were performed using solutions of the test material made up in carbon filtered tap water at mean measured concentrations of 0 (control), 0.98, 2.26, 4.12, 5.6, and 22.69 mg/L. The tests were conducted in a semi-static (renewal) system over a 96 hour period

at a controlled temperature of 26.5°C, with water removed daily and replaced with fresh water containing the respective concentrations of the test material. Solution analysis was conducted daily by gas chromatography for determination of the test chemical concentrations. Seven fish were tested at each concentration. During these tests the pH of the test solutions remained between 7.4 and 8.0, dissolved oxygen levels remained between 6.8 and 7.2 mg/L and water hardness remained between 138 and 155 mg/L as $CaCO_3$.

No fish mortality occurred over the duration of the test for concentrations less than or equal to 5.6 mg/L, while at the highest concentration tested (22.7 mg/L) all fish died immediately. Behavioural aberration, specifically erratic swimming activity, was observed at concentrations greater than or equal to 2.26 mg/L. The tests results indicate that the material Opalal is moderately toxic to zebra fish with a 96 hour LC_{50} = 11.27 mg/L, and NOEC (96 h) between 0.98 and 2.26 mg/L.

The acute immobilisation tests on *Daphnia* were performed using solutions of the test material in a static non renewal system over a 48 hour period at a controlled temperature of 20 ±2 °C. Five solutions of the chemical with (geometric mean) measured concentrations of 0.69, 1.6, 3.4, 6.8 and 11 mg/L were tested, together with one control. Solution analysis (gas chromatography) for the test compound was conducted daily on samples of both old and fresh test media. Five juvenile *Daphnia* were tested at each concentration, with four replicate tests conducted at each concentration. During these tests the pH of the test solutions remained between 7.4 and 8.0, while dissolved oxygen levels remained between 7.8 and 9.0 mg/L and hardness was approximately 240 mg/L as $CaCO_3$.

Significant reduction in *Daphnia* mobility was observed during the tests, and the results indicate that the material Opalal is at most moderately toxic to *Daphnia* with a 48 hour NOEC = 3.4 mg/L.

A test on the inhibition of algal growth was also conducted on the freshwater green algae *Scenedesmus subspicatus* over a 72 hour incubation period at 21-24°C with (geometric mean) measured concentrations for the test material of 0.73, 1.1, 3.4, 3.6 and 8.5 mg/L, together with a control containing no chemical. The solutions were made up in distilled water. The measured test concentrations were significantly less than the nominal concentrations (up to 90 % difference), indicating appreciable adsorption of the test material by the algal mass. Both rate of growth and algal biomass were monitored over the 72 hour test duration, and the results show the new chemical to be moderately toxic to this species of green algae, with an approximate EC_{50} of 8.2 mg/L, and NOEC (72 h) = 3.6 mg/L based on the biomass data.

The new chemical was also studied for its effect on the respiration of sewage bacteria, and was found to have some inhibitory effects at concentrations equal to or greater than 100 mg/L. In contrast, the reference material used in these tests, 3,5-dichlorophenol, produced 89 % inhibition of bacterial respiration at a concentration of 32 mg/L. The compound is therefore considered to be practically non toxic to these bacteria.

The QASR calculations of the ASTER database (US Environment Protection Authority, 1998) also furnished predicted acute toxicity LC_{50} data for several fish species which included

Rainbow trout (2.92 mg/L), Fathead minnow (7.38 mg/L), Bluegill (6.0 mg/L), and Channel catfish (3.2 mg/L). These calculations also furnished an acute LC_{50} of 4.3 mg/L for immobilisation of *Daphnia*, and a chronic MATC of 1.18 mg/L for Fathead minnow. These results are in reasonable accord with the experimental data, and support the conclusion that the new chemical can be considered to be moderately toxic to aquatic species.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The majority of the new chemical is an ingredient of domestic cleaning formulations and most of the material would eventually be released into domestic sewage systems as a consequence of product use. However, due to the volatility of the material, a high proportion is likely to enter the atmosphere where it is expected to be degraded through reactions with hydroxyl radicals.

The ecotoxicity data indicates that the new chemical can be considered moderately toxic to aquatic species. Based on annual imports of 0.5 tonne, all of which is eventually released to sewer, the daily release on a nationwide basis is 1.36 kg/day. Assuming a national population of 18,000,000 and that each person contributes an average 150 L/day to overall sewage flows, the predicted concentration in sewage effluent on a nationwide basis is estimated as 0.5 µg/L. When released to receiving waters the concentration is generally understood to be reduced by a further factor of at least 10, and so the Predicted Environmental Concentration is around 0.05µg/L. This is several orders of magnitude less than the concentrations at which the compound has demonstrated toxicity to aquatic species.

The chemical is hydrophobic with Log K_{ow} = 5.33. This indicates high affinity for organic material, although the measured value of Log K_{oc} = 2.6 indicates only moderate affinity for the organic component of soils and sediments. The Simple Treat and Level 1 Mackay calculations also indicate that due to the relatively high vapour pressure, much of the chemical would partition into the atmosphere and be destroyed by reactions with hydroxyl free radicals. Nevertheless, it is likely that some of the chemical would become bound to soils and sediments, and here it would be expected to be slowly degraded to water, carbon dioxide and methane through biological processes. These mechanisms would operate to continuously remove the chemical from the environmental compartments, and that overall environmental concentrations would be unlikely to increase with prolonged release of the chemical.

The above considerations indicate a low hazard to the environment when the new chemical is used as a component of domestic products in the manner indicated by the notifier.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The notified chemical is of low acute toxicity, but is a moderate skin irritant and a slight eye irritant in rabbits. The main hazards associated with the public and occupational use of Opalal will be associated with the irritant properties. A NOEL could not be established for the

chemical.

The notified chemical will be imported in mixtures as compounded fragrances containing high concentrations (up to 25 %) of the notified chemical. The fragrances will be used in the manufacture of consumer products, where the final concentration of the notified chemical will be much lower. Therefore the irritant effects will be of most concern in the industrial use of the chemical.

The fragrance mixtures containing Opalal are to be sold on to a variety of customers; the notifier was able to provide only basic information on the manufacturing processes whereby the notified chemical will be incorporated into a variety of consumer products. All potential product types are not determined, however. The notifier provided examples of the manufacturing processes involved in the manufacture of air fresheners and solid and liquid soaps, which are examples of the types of products in which these fragrances may be used. The processes will generally be automated sealed systems. After formulation of the products, the occupational exposure, for example for packaging workers, should be low.

Dermal exposure to spills and drips on the transfer of the compounded fragrances are likely to be the main route of exposure for production workers. This is most likely to occur on connecting and disconnecting the 200 L drums of fragrance, and when cleaning the production equipment and empty drums. Inhalation exposure is also possible, although the vapour pressure of the notified chemical is low (1.4×10^{-2} kPa at 25 °C). Workers may also be exposed to the notified chemical when using the retail products. Exposure and risk for these workers would be similar to that for the general public.

The notifier recommends that impervious gloves and eye protection be worn when the concentrated material is handled, and indicates that adequate ventilation should be provided at all times, including local exhaust ventilation during filling operations. Workers involved in the manufacture of consumer products will need to be protected against the topical and systemic effects of repeated exposure. The chemical is a hazardous substance and warrants the risk phrase R38 'Irritating to skin', as the chemical produced persistent skin irritation. This information is provided on the label for the notified chemical. The imported fragrances containing the chemical at up to 25 % will be hazardous substances in relation to the chemical when it is present at ≥ 20 %. In addition, a no effect level could not be established for the chemical. Consequently, workers repeatedly handling the imported fragrances, or end use products containing high concentrations of the notified chemical, will require skin protection.

As the notified chemical will be used in a wide range of household products, there will be widespread public exposure. However, the public health hazards associated with skin and eye irritation are likely to be offset by the low concentration of 0.001 – 0.5 % of the notified chemical in household products.

The notifier has supplied a risk assessment where typical exposures from cosmetic products, soaps/shower gels, and household products have been calculated based on European usage figures. Assuming a notified chemical concentration of 0.03 % in household products, and 0.006 % in cosmetic products and soaps/shower gels, 10 % absorption through the skin, and a

60 kg body weight, a person applying 10 g of cosmetic cream, once daily, would receive a systemic exposure of 0.001 mg/kg/day. A person using 5 g of soap/shower gel per day, assuming 10 % remains on the skin, would receive a systemic exposure of 0.00005 mg/kg/day, and a person using 10 g of a household product, 1 % of which is in direct contact with the skin, would receive a systemic exposure of 0.00005 mg/kg/day. The total estimated exposure is thus of the order of 0.001 mg/kg/day. Therefore public exposure from the proposed use is likely to be low.

Based on the use pattern for the notified chemical it is considered that it is unlikely to pose a significant hazard to public health.

13. RECOMMENDATIONS

To minimise occupational exposure to Opalal 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 3765.2 (Standards Australia, 1990);
- Impermeable gloves should conform to AS/NZS 2161.2 (Standards Australia/Standards New Zealand, 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;
- Good personal hygiene should be practised to minimise the potential for ingestion;
- A copy of the MSDS should be easily accessible to employees.
- Imported compounded fragrance products containing the notified chemical at ≥ 20 % will need to conform with the NOHSC *National Code of Practice for the Labelling of Workplace Substances*.

14. MATERIAL SAFETY DATA SHEET

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

Health and Safety Commission, 1994b).

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 chemical shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise. No other specific conditions are prescribed.

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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