File No: NA/668

September 1999

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Magnol-R

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Director
Chemicals Notification and Assessment

Magnol-R

1. APPLICANT

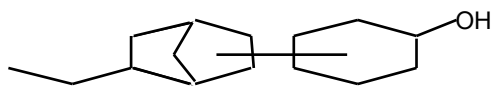
Kao (Australia) Marketing Pty Ltd of 103 Yerrick Road LAKEMBA NSW 2195 has submitted a limited notification statement in support of their application for an assessment certificate for Magnol-R.

No claim was made for exempt information.

2. IDENTITY OF THE CHEMICAL

Chemical Name:	Phenol, 2-methoxy-, reaction products with 5-ethylidenebicyclo [2.2.1]-hept-2-ene, hydrogenated
Chemical Abstracts Service (CAS) Registry No.:	224790-80-1
Marketing Name:	Magnol-R
Molecular Formulae:	$C_{15}H_{26}O$
Molecular Weight:	222

Structural Formula



Method of Detection and Determination:	ultraviolet-visible (UV/Vis), infrared (IR), nuclear magnetic resonance (NMR); and gas liquid chromatography (GLC)
Spectral Data:	UV/Vis: the notified chemical in ethanol exhibited an absorbance peak at 277 nm; IR: the 10 strongest peaks were 1 327, 1 306, 1 264, 1 215, 1 192, 982, 912, 855, 783 and 731 cm^{-1}; the peak at 3405 was ascribed to OH, those at 2 936, 2867 to CH, CH_2, CH_3 and 1453 to CH, CH_2 and that at 1 264 to CH, CH_2, CH_3 NMR: ^{1}H-NMR was provided

Comments on Chemical Identity

The notified chemical is a UVCB comprising over 50 chemical entities, with the structural formula of four main components depicted above. The compounds are synthesised as a result of the hydrogenation of the adducts formed between ethylidenebicyclo [2,2,1]-heptene and 2-methoxy phenol.

The notifier provided comprehensive spectroscopic data – infra red, UV/visible, and NMR – on the notified substance, which may be used to identify the material. A Gas Liquid Chromatogram also accompanied the notification.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	colourless, viscous liquid
Boiling Point:	decomposes before boiling point is reached
Pour Point:	0°C
Specific Gravity:	1.049 at 20°C
Vapour Pressure:	0.111 x 10^{-3} kPa at 25°C, see comments below
Water Solubility:	0.03 g/L at 20°C, see comments below
Henry's Law Constant:	0.82 Pa/m^3/mole, see comments below
Partition Co-efficient (n-octanol/water):	log P_{ow} = 4.18 at 21°C, see comments below

Hydrolysis as a Function of pH:	Test not conducted, see comments below
Adsorption/Desorption:	Log K_{oc} 1. 2.67 Log K_{oc} 2. 2.76 Log K_{oc} 3. 2.91 Log K_{oc} 4. 2.98 Log K_{oc} 5. 3.05
Dissociation Constant:	Test not conducted, see comments below
Surface Tension:	49.22 mN/m at 23°C
Particle Size:	Not applicable as substance is a liquid
Fat Solubility:	totally miscible at 37°C
Flash Point:	118°C (closed cup)
Flammability:	not flammable according to EC testing; combustible
Autoignition Temperature:	265°C
Explosive Properties:	not explosive according to EC testing

Comments on Physico-Chemical Properties

Tests were performed according to standard OECD/EC test methods. Full test reports were provided.

The notified chemical is considered to be volatile based on its vapour pressure (Mensink, 1995).

Water solubility was determined by stirring an excess of the test substance with 100 mL of distilled water at 30°C for three days, equilibrating for one day at 20°C, then separating the aqueous and non aqueous layers in a separating funnel. The content of the notified substance was then determined by gas chromatography.

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) x Vapour Pressure (Pa)/Water solubility (g/L).

The results also suggest a potential for volatility (Mensink, 1995).

Compound 4 of the notified substance carries a methoxy group that may be susceptible to hydrolysis under extreme conditions but is not expected to do so under environmental pH range of 4 to 9. Compounds one to three are unlikely to be susceptible to hydrolysis.

The n-octanol/water partition function was determined using the shake flask method, with analyses performed by gas chromatography. The determined value of log P_{ow} indicates the notified substance has a high affinity for hydrocarbon like environments.

In the high performance liquid chromatography (HPLC) method used for estimating the soil adsorption coefficient, 5 main peaks were observed. Log K_{oc} for the 5 main peaks show that the notified substance is likely to have medium mobility in soil for the first peak and low mobility in soil for the remaining four.

The compound contains no functionalities capable of readily dissociating in aqueous media, so dissociation constant data are not applicable and were not provided.

The notified substance is completely soluble in fat, which is in accord with the high log P_{ow}.

The material is surface active. The surface tension of an aqueous solution containing approximately 25 mg/L (90% saturation) of the test substance was 49.22 mN/m at 23°C. By definition, a chemical has surface activity when the surface tension is less than 60 mN/m (European Commission, 1992).

4. PURITY OF THE CHEMICAL

Degree of Purity: 100%

Additives/Adjuvants: triethyl citrate (CAS# 77-93-0)

5. USE, VOLUME AND FORMULATION

The notified chemical is to be used as a fragrance enhancer in a wide variety of domestic consumer products including detergents, fabric softeners, soaps and cosmetics. It will be imported at 0.1 tonne in the first year increasing to 0.3 tonne per annum by 2002.

The notified chemical (Magnol-R) will not be manufactured in Australia but will be imported as a formulation (Magnol, containing 50% w/w of the notified chemical in triethyl citrate) in sealed, unbreakable lacquered steel drums of 30 L or 200 L capacity.

The notified chemical is blended into a formulated perfume, which is then incorporated into household products at a maximum concentration of 0.1%.

6. OCCUPATIONAL EXPOSURE

Transport and Storage
Worker exposure during transport or storage of Magnol is not expected except in the event of accidental spillage.

Manufacturing Process,
The notifier indicates that no specific reformulation sites have been identified. Process descriptions, therefore, present both possible scenarios of automated and non-automated plants.

Manufacturing Process - Formulation of the Preparation (Perfume)
Magnol (50%), in liquid form, is either manually or automatically weighed and charged to a mixer to be blended into a formulated perfume at a concentration of 0.1 to 5%. The mixing process can be of variable batch sizes: 25 kg, 50 kg, 100 kg, 500 kg or 1 tonne. Following mixing, the preparation is discharged, via an automated process, into containers. Raw material quality control testing (sampling, analysis and odour evaluation) of Magnol occurs before formulation.

The mixing phase is attended to by a single worker for 2 to 3 minutes per day. Up to 3 workers may be involved in quality control for a total of 6 to 9 minutes per day. Discharge (filling of containers) involves one worker for 5 minutes per day.

During the mixing and discharge phases exposure to spills is possible. Some exposure to the preparation could occur during quality control testing. The mixing vessels are stated to retain 0.05% of the formulation (maximum 0.5 kg per batch) so during wash-down, exposure to small amounts of the notified chemical may occur.

Manufacturing Process - Formulation of Consumer Product
Formulators of detergents, toiletries etc have not been identified at this stage. However, depending on the facilities of the formulator, the perfume preparation is either manually or automatically charged to a mixer to give the final domestic product; the perfume preparation containing the notified chemical is present in consumer products at a maximum concentration of 0.1%. The final product is then discharged, typically via an automated process, into various types of retail size containers.

Sources of exposure to the notified chemical will be the same as identified above (that is, spillages), however, the notified chemical will be present at a lower concentration.

End Use
Workers, for example commercial cleaners, may receive exposure to the notified chemical through use of the final product. Exposure is expected to be negligible given the low concentration of notified chemical in the final product.

Prevention of Worker Exposure
The notifier's recommendations for formulation include the wearing of cuffed butyl rubber gloves, goggles, plastic face shields, aprons and boots in addition to use of local exhaust ventilation and splash proof filling devices to prevent contact with the notified chemical.

Education and Training
The notifier indicates that workers receive training, including training on procedures for handling chemicals.

7. PUBLIC EXPOSURE

The notified chemical will enter the public domain at a low concentration (up to 0.1%) in household products (for example, detergents, toiletries, cosmetics) containing it. Although the public will make contact dermal and inhalation contact, and possibly eye contact with these products (for example, while using shampoos containing the notified chemical), exposure is likely to be low because of the low concentration of the notified chemical in the products. The potential for public exposure to the notified chemical during transport, reformulation and disposal is assessed as negligible.

8. ENVIRONMENTAL EXPOSURE

Release

Table 1 gives estimates of release for each processor and user waste stream.

Table 1. Process waste release to compartments

	Waste stream		
Process	***Total***	***Incinerator or Landfill***	***Sewer***
	Kg	***Kg***	***Kg***
Blending perfume mix	0.15	0.141	0.009
Production of final use product	0.03	0.028	0.002
Spillage	3.0	2.820	0.18
Drum disposal	0.15	0.15	-
Domestic use (assumption)	296.67	-	296.67
Totals to compartments	300	3.14	296.86

The notified chemical is used to prepare perfume blends, which are subsequently blended into soaps, detergents, fabric softeners and other household products. The notifier indicates that these production activities would be performed by a number of different companies. However, it is expected that production activities will takes place in purpose constructed

facilities, and the notifier has estimated release to the environment during perfume blending and manufacture of the final products.

The notifier indicates that during blending of the perfume mixture, 0.05% of the notified chemical is lost during washing out of mixing vessels. On an annual basis, this amounts to a maximum release of 150 g. The notifier also stated that material released as a result of equipment washing (and presumably spillage) is sent with other waste to on-site treatment facilities. These may include unit operations such as dissolved air flotation and granulated carbon filters. The notifier states that 94% (approximately 141g per annum) of the notified substance would be removed from the waste water by this treatment, become incorporated into the solid waste stream and incinerated. The treated waste water, containing the remaining 6% (annually around 9 g) of notified chemical, is presumably discharged to the sewer.

The notifier indicates that no liquid waste streams are produced during production of the consumer products into which the perfume blend is added, but that around 0.01% of the notified substance (annually 30 g) may be lost as a consequence of steam cleaning the mixing vessels at product changeover. Presumably this would also be sent to the water treatment plant where 94% (annually 28g) would become incorporated in solid residuals and incinerated.

No reference to the quantities of notified chemical likely to be lost and released as a result of accidental spillage was made in the submission. However, it is estimated that if as a worst case, 1% of total import quantity was lost through accident (annual release of around 3 kg), cleaned up with water then diverted to wastewater treatment at the manufacturing site where 94% of the chemical is removed then incinerated, an estimated 180 g of chemical would remain to be released to the sewerage.

It is likely that the empty steel drums would be placed into landfill. No estimates of the amount of residual chemical left in the drums was provided, however if this amounted to 0.05% of the import quantity, or around 150 g per annum would be placed into landfill.

The majority of the notified chemical used as a fragrance enhancer in domestic cleaning products, is likely to be released into the environment as a consequence of normal product usage. This release would be primarily to the sewerage system, where some adsorption to sludge would be expected. Empty containers of consumer products are likely to contain minor amount of residual unused product. These packages would be discarded with domestic garbage and disposed of into landfill.

Fate

The notifier provided a biodegradation study of the notified chemical, conducted in accordance with the OECD Test Guideline TG 301E (Closed Bottle Test). The test indicated 0.8% loss of initial COD of the test material after 28 days, therefore, the notified chemical cannot be classed as readily biodegradable.

All the notified chemical will eventually be released into the environment (see Table 1), and the majority (approximately 99%) could be expected to be discharged into sewerage systems.

For that proportion of the chemical which reaches sewage treatment plant, unchanged, the Simple Treat Model (European Commission, 1996) is used to estimate partitioning in the environment. Estimates are based on the chemical having a calculated Henry Law Constant of 0.85 Pa.m^3/mole, and being not biodegradable. The results indicate that the chemical would be expected to partition into the air, water and sewerage plant sludge as follows:

Air	*Water*	*Sewerage Plant Sludge*
0%	56%	44%

The partitioning to sludge is consistent with the notified chemical's hydrophobic character (log P_{ow} = 4.18), surface activity (< 49.22 mN/m) and estimated log K_{oc} of 2.67 to 3.05. It is therefore likely to eventually become incorporated into sediments, where it would be slowly degraded through biological processes to water, carbon dioxide and methane. The proportion of the notified chemical entering the water phase is likely to be highly diluted, but in practice the movement of the effluent stream exposes the notified chemical to more sediment than the equilibrium conditions in the above model. The notified chemical would be more likely to eventually partition to the sediment.

Residual chemical will be found in empty drums, discarded consumer packaging or in solids derived from water treatment at the production facilities. Residual chemical disposed of to landfill 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 notified chemical exhibits a lipophilic nature that suggests some potential for bioaccumulation. However, the surface activity and potential for adsorption to soil and sediment with consequent degradation, should prevent any bioaccumulation.

9. EVALUATION OF TOXICOLOGICAL DATA

The notifier has provided the following toxicity data in support of their application.

9.1 Acute Toxicity

Summary of the acute toxicity of Magnol-R

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} > 5 300 mg/kg for males LD_{50} > 4 200 mg/kg for females	(Kynoch, 1984b)
acute inhalation toxicity	rat	LC_{50} > 5.4 mg/L/4 hour	(Jackson, 1985)
acute dermal toxicity	rat	LD_{50} > 2 000 mg/kg	(Kynoch, 1984a)
skin irritation	rabbit	slight to moderate, delayed, irritant	(Liggett, 1984a)
eye irritation	rabbit	slight to moderate irritant	(Liggett, 1984b)
skin sensitisation:	guinea pig		
. maximisation test with Magnol R:		sensitiser	(Seaber, 1984)
. Buehler method with Magnol R:		sensitiser	(Takahashai, 1995)
. Buehler method with Magnol*:		non-sensitising	(Takahashai, 1996)

* Magnol is 50% Magnol R in solvent, triethyl citrate.

9.1.1 Oral Toxicity (Kynoch, 1984b)

Species/strain: rat/ Sprague Dawley

Number/sex of animals: 5/sex per group (3 dose groups)

Observation period: 15 days

Method of administration: a single dose of 3 200 mg/kg, 5 000 mg/kg or 8 000 mg/kg administered by gavage to each group

Test method: OECD TG 401

Clinical observations:
Shortly after dosing, pilo-erection, hunched posture, abnormal gait, lethargy, pallor of the extremities, diarrhoea and increased salivation, noted in all rats. These signs were accompanied by decreased respiratory rate in one rat treated at each of 3 200 mg/kg and 8 000 mg/kg and four rats treated at 5 000 mg/kg; comatose like condition in five rats treated at 3 200 mg/kg and six rats treated at 8 000 mg/kg. Recovery was complete by Day 8

Mortality:
The number of deaths/dose group: 3/3 200 mg/kg; 4/5 000 mg/kg; and 9/8 000 mg/kg, and occurred within 22 hours and 4 days of dosing; body weight losses were recorded for these animals.

Morphological findings:
Terminal autopsy findings were normal. Autopsy findings of in-study decedents included congestion of the lung, pallor of the liver and spleen, and red or brown fluid-filled contents of the intestine

LD_{50}:
4 700 mg/kg acute median lethal dose for males and females;
5 300 mg/kg acute median lethal dose for males;
4 200 mg/kg acute median lethal dose for females.

Result:
The notified chemical was of very low acute oral toxicity in rats.

9.1.2 Inhalation Toxicity (Jackson, 1985)

Species/strain: rat/HC/CFHB (Wistar)

Number/sex of animals: 5/sex per group

Observation period: 14 days

Method of administration: a single dose of 0 or 5 mg/L, whole body exposure; mean aerosol concentration in chamber air was 5.40 mg/L

Particle size distribution: Approximately 91% of the test substance was of respirable particle size, < 5.5 μm aerodynamic diameter

Test method: OECD TG 403

Mortality: nil

Clinical observations:
During the exposure period:
Closing or partial closing of the eyes, abnormal breathing, abnormal body posture and a reduced response to external stimuli were observed.

During the observation period:
Red-brown staining around the snout and jaws, abnormal breathing, râles and an oily appearance of the body fur were noted for all rats upon removal from the test chamber; râles was evident on the day following exposure and abnormal breathing was observed for 8 days post exposure. The red-brown staining persisted in male rats for 6 days and in female rats for up to 11 days post exposure.
Moderate reductions of bodyweight or in the rate of bodyweight gain for 3 to 4 days following exposure; subsequently the rate of bodyweight gain was similar to that of the control rats.
Marked to moderate reduction in food consumption of male and female rats for 3-4 days following exposure; food consumption for male rats remained below that of the control rats until Day 9.
Water consumption was reduced for 2 days following exposure to the test substance.

Morphological findings:
Macroscopic and microscopic findings were not considered to be related to treatment.

LC_{50}:
> 5.40 mg/L/4-hour

Result:
The notified chemical was of very low acute inhalation toxicity in rats.

9.1.3 Dermal Toxicity (Kynoch, 1984a)

Species/strain: Rat/ HC/CFY (Remote Sprague Dawley)

Number/sex of animals: 5/sex

Observation period: 14 days

Method of administration: a single dose of 2 000 mg/kg was applied to an intact skin site and covered with semi-occlusive dressing; after 24 hours the dressing and residual test material were removed

Test method: limit test - OECD TG 402

Mortality: nil

Clinical observations:
On Day 5 slight to well defined erythema and oedema was observed in all animals which persisted to Day 7 and returned to normal on Day 8 with some residual dryness and sloughing of the epidermis in one animal.

Morphological findings:
No abnormalities detected.

LD_{50}:
> 2 000 mg/kg

Result:
The notified chemical was of low dermal toxicity in rats

9.1.4 Skin Irritation (Liggett, 1984a)

Species/strain: rabbit/New Zealand White

Number/sex of animals: 3 males

Observation period: 9 days

Method of administration: 0.5 ml of the test substance was applied to an intact skin site; the site was covered with occlusive dressing; after 4 hours the dressing and residual test substance were removed

Test method: OECD TG 404

Draize scores:

	Time After Treatment (Days)								
Animal	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***
Erythema									
1	0	0	0	2	2	1	1#	1#	0
2	0	0	0	1	1	1	1#	0	-
3	0	0	0	1	1	1	1#	0	-
Oedema									
1	0	0	0	1	2	1	1	0	0
2	0	0	0	0	0	0	0	0	-
3	0	0	0	0	0	0	0	0	-

[1] see Attachment 1 for Draize scales. # desquamation

Comment:
Day 4: slight oedema was observed in one animal, which persisted up to Day 7.
On Day 4 slight to well defined erythema were observed in all 3 animals which persisted up to Day 7.
On Day 7 desquamation of the stratum corneum was observed in all 3 animals which persisted to Day 8 in one animal

Result:
The notified chemical was a slight to moderate, although delayed, irritant to the skin of rabbits.

9.1.5 Eye Irritation (Liggett, 1984b)

Species/strain: rabbit/New Zealand White

Number/sex of animals: 3 males

Observation period: 7 days

Method of administration: 0.1 mL of the test substance was instilled in the conjunctival sac of one eye of each rabbit whilst the contralateral eye served as the control

Test method: OECD TG 405

Draize scores of nonirrigated eyes:

	Time after instillation															
Animal	***1 hour***			***1 day***			***2 days***			***3 days***			***4 days***			***7 days***	
Cornea																	
1	0			1			1			0			0			0	
2	0			1			1			0			0			0	
3	0			1			1			0			0			0	
Iris																	
1	0			0			0			0			0			0	
2	0			0			0			0			0			0	
3	0			1			0			0			0			0	
Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***
1	1	2	N	2	1	N	2	1	N	1	0	N	0	0	N	0	0
2	1	1	N	2	1	N	2	1	N	1	1	N	1	0	N	0	0
3	2	1	N	2	1	N	2	1	N	1	0	N	0	0	N	0	0

[1] see Attachment 1 for Draize scales
r = redness c = chemosis d = discharge. N= not reported.

Comment:
Corneal opacities were observed in all three animals, which were resolved by Day 3.
Iridial inflammation was observed in one animal up to Day 1.
Diffuse crimson – red colouration of the conjunctivae was seen in all three animals; considerable swelling with partial eversion of the eyelids was seen in one animal at the one hour reading.

Result:
The notified chemical was a slight to moderate irritant to the eyes of rabbits.

9.1.6 Skin Sensitisation Studies

9.1.6.1 Skin Sensitisation Magnusson and Kligman Maximisation Method (Seaber, 1984)

Test method: Similar to OECD TG 406

Species/strain: guinea pig/Dunkin Hartley

Number of animals: 20 females (test group), 10 females (control group)

Test Substance: Magnol R

Induction procedure:

test animals:
Day 1: three pairs of intradermal injections (0.1 mL) into the dorsal skin of the scapular region:

- Freund's complete adjuvant (FCA) 1:1 in water for irrigation
- the test substance, diluted to 2.5% v/v in liquid paraffin
- the test substance at 2.5% v/v emulsified in a 50:50 mixture of FCA and liquid paraffin;

Day 7 - filter paper saturated with the test substance as supplied was applied to the treated area and held under occlusive dressing for 48 hours;

control animals:
treated similarly to the test animals omitting the notified chemical from the intradermal injections and topical application

Challenge procedure:

test and control animals:
Day 21: filter paper saturated with 20% v/v or 10% v/v test substance in liquid paraffin, was applied to the anterior flank and posterior flank, respectively, and held under occlusive dressing for 24 hours;

Number of Animals Exhibiting Positive Responses Following Challenge:

Challenge concentration	***Test animals***			***Control animals***		
	24 hours*	***48 hours****	***72 hours****	***24 hours***	***48 hours***	***72 hours***
20%	**17/20	12/20	6/20	1/10	0/10	0/10
10%	14/20	4/20	3/20	1/10	0/10	0/10

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

Challenge Outcome:
Challenge concentration of 20%: 12 animals had slight erythema and one of the 12 had slight oedema at the 48 hour observation time (72 hours from the start of challenge).
Challenge concentration of 10%: 4 animals had slight erythema and one of the 4 had slight oedema at the 48 hour observation time (72 hours from the start of challenge).

Comment:
The study authors provided the following commentary on the dermal reactions observed in test animals: reactions of similar intensity were observed for test and control animals at 24 hours. At 48 hours, 4 test animals gave only localised responses, and for 3 test animals reactions were only observed at the anterior site. These reactions were not considered to represent sensitisation. At 72 hours dermal responses persisted in 4 test animals, therefore these test animals were considered to give positive responses. Reactions for one animal had subsided to being localised, therefore this animal was considered to give an inconclusive response.

It was concluded that delayed contact hypersensitivity was evident in four animals, an inconclusive result was shown in one animal and no evidence of delayed contact hypersensitivity was seen in the remaining 15 test animals. Magnol-R is considered to have the potential to cause skin sensitisation based on the overall higher incidence and persistence of dermal reactions observed for test animals when compared to the control animals at challenge.

Result:
Magnol-R was sensitising to guinea pig skin.

9.1.6.2 Skin Sensitisation - Buehler Method on Magnol R (Takahashai, 1995)

Species/strain:	guinea pig/Hartley
Number of animals:	10 females (test group), 5 females (control group)
Test substance:	Magnol-R
Test method:	Similar to OECD TG 406
Induction procedure:	test animals: Days 1, 7 and 14: 0.5 mL of neat Magnol R applied to a lint pad and placed on the clipped back shoulder and held under occlusive dressing for 6 hours; control animals: treated similarly to the test animals, but Vaseline was used in place of the test substance
Challenge procedure:	test and control animals: Day 28: 0.1 mL each of 0% (vaseline), 5%, 10% or 30% Magnol in vaseline was applied on the cloth area of an adhesive tape, and placed on various sites on the animals and held under occlusive dressing for 6 hours; inspection and recording of dermal responses occurred 24, 48 and 72 hours post exposure

Number of animals exhibiting positive responses at challenge:

Challenge concentration	Test animals			Control animals		
	24 hours*	48 hours*	72 hours*	24 hours	48 hours	72 hours
30%	**3/10	3/10	3/10	0/5	0/5	0/5
10%	0/10	0/10	0/10	0/5	0/5	0/5
5%	0/10	0/10	0/10	0/5	0/5	0/5
0%	0/10	0/10	0/10	0/5	0/5	0/5

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

Challenge outcome:
Challenge concentration of 30%: 2 animals had well defined erythema and one animal had very slight erythema, which persisted to the 72 hour observation time.
Challenge concentrations of 0, 5, or 10% revealed no discernable reactions.
Control group - no discernable reactions.

Result:
Magnol R was sensitising to guinea pig skin.

9.1.6.3 Skin Sensitisation Buehler Method on Magnol (Magnol-R and Triethyl Citrate 50:50 w/w%) (Takahashai, 1996)

Species/strain:	guinea pig/Hartley
Number of animals:	10 females (test group), 5 females (control group)
Test substance:	Magnol (Magnol-R and Triethyl Citrate 50:50 w/w%)
Test method:	Similar to OECD TG 406
Induction procedure:	test animals: Days 1, 7 and 14: lint cloth soaked with 0.5 mL of 5% Magnol in vaseline was applied to the shorn left ventral skin and held under occlusive dressing for 6 hours; control animals: treated similarly to the test animals omitting the test substance from the topical application

Challenge procedure:	test and control animals: Day 28: 0.1 mL each of 1%, 3% or 5% Magnol in vaseline was spread on the surface of a round patch; the patches were applied to the shorn right ventral skin of the animal and held under occlusive dressing for 6 hours; Inspection and recording of dermal responses occurred 24, 48 and 72 hours post exposure

Challenge outcome:
No discernable reactions were observed at the 24, 48 or 72 hour observation period

Result:
Magnol was non sensitising to guinea pig skin.

9.2 Genotoxicity

9.2.1 *Salmonella typhimurium* Reverse Mutation Assay (Kitching, 1995)

Two independent main mutation assays were performed, in the presence and absence of an external metabolic activation system.

In the first mutation assay, an increase in revertant colony numbers was observed with *Salmonella typhimurium* strain TA 100 at the highest non toxic dose (1 500 µg/plate).

In the second mutation assay, toxicity was observed at this dose level (1 500 µg/plate) and no increases revertant colony numbers were observed. As no definite conclusion could be drawn about the effect on TA 100, additional tests were conducted using different dose levels and conditions to investigate whether the increases observed in the first assay were due to a mutagenic response. Toxicity was observed down to 500 µg/treatment mixture. There were no significant increases in revertant colony numbers observed in these additional tests.

First Mutation Assay:

Strains:	TA 1535, TA 1537, TA 98 and TA 100
Concentration range:	0, 50, 150, 500, 1 500 and 5 000 µg/plate
Metabolic activation system:	liver fraction (S9 mix) from rats pretreated with Aroclor 1254
Test method:	OECD TG 471

Comment:
Toxicity of the notified chemical was noted at 5 000 µg/plate. An increase in revertant colony numbers was observed with TA 100 at the highest non toxic concentration (1 500 µg/plate) both in the presence or absence of metabolic activation. Positive controls gave the expected responses.

Second Mutation Assay:

Strain:	TA 100
Concentration range:	Test 1: 0, 250, 500, 1 000, 1 500, 2 500 µg/plate; Test 2: 0, 25, 50, 100, 250, 500, 750, 1 000, 1 500, 2 500 5 000 µg/plate
Metabolic activation system:	liver fraction (S9 mix) from rats pretreated with Aroclor 1254
Test method:	in house investigation

Comment:
Toxicity was observed at 250 µg/plate and above; no significant increases in colony numbers was observed. Positive controls gave the expected responses.

Result:
The notified chemical was not mutagenic in this bacterial assay.

9.4 Overall Assessment of Toxicological Data

In support of their application, the notifier provided the following animal studies: acute oral, inhalation and dermal toxicity, skin and eye irritation and skin sensitisation studies (Magnusson and Kligman Maximisation Test and Buehler Test). A skin sensitisation study (Buehler method) was provided for Magnol (Magnol R in triethyl citrate). For investigation of mutagenicity an Ames test was provided.

The notified chemical was of very low acute oral (LD_{50} = 4 700 mg/kg) and very low acute inhalation toxicity (LC_{50} > 5.4 mg/L/4 hour). However, mortality occurred in the acute oral test and clinical signs suggestive of neurotoxicity were observed in both the oral and inhalation studies and it is noted that in 1994, the acute oral and inhalation studies were submitted by Kao Corporation of America to the US EPA (under TSCA Section 8e) to report possible neurological effects which might result from over exposure to the notified chemical. Rats exhibited skin irritation, which persisted for 8 days, following topical application of the notified chemical in the acute dermal toxicity test (LD_{50} > 2 000 mg/kg). In rabbits, the notified chemical was a slight to moderate, although delayed, skin irritant and slight to moderate eye irritant. Magnol R was sensitising to guinea pig skin in both adjuvant and non adjuvant test methods. Magnol was not considered a skin sensitiser in a non-adjuvant type test, however, the concentration of notified chemical used in this study was low (2.5%).

Mutagenic activity although observed in an initial bacterial mutation assay was not observed in repeat investigations using a range of dose levels and conditions. Because of the absence of mutagenic activity in follow-up studies, it was concluded the notified chemical did not exhibit mutagenic activity in the bacterial system tested. No other mutagenicity data was provided.

The results of the acute oral, inhalation and dermal studies in rats and the skin and eye irritant studies in rabbits are below the thresholds for classification as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999) for the toxicological end points assessed. The notified chemical was not considered mutagenic in a bacterial mutation assay. The notified chemical exhibited positive responses in both adjuvant and non adjuvant type tests for skin sensitisation. The percentage of animals showing evidence of delayed contact hypersensitivity in both studies met the criteria for classification as skin sensitiser under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999). Therefore, the overall hazard classification for the notified chemical is Irritant (Xi) with risk phrase R43 – May Cause Sensitisation by Skin Contact.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The notifier has provided the following ecotoxicity data in support of the application. Ecotoxicity tests were performed in accordance with OECD Test Guidelines (OECD, 1995-1996).

Test	*Species*	*Results (Nominal)*
Acute Immobilisation [OECD 202]	*Daphnia magna*	EC_{50}(48 h) = 1.5 mg/L NOEC(48 h) = 0.22 mg/L

Ten daphnia were tested at each concentration, with each test performed in duplicate. During the tests the pH of the test solutions remained between 7.5 and 7.8, while dissolved oxygen levels (measured for the control only) remained between 7.2 and 8.6 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 21°C. Five solutions of chemical with measured concentrations of 0.097, 0.22, 0.4, 0.88, 1.9, 4.0 and 8.8 mg/L were tested, together with one control. Solution analysis was conducted daily by extraction with dichloromethane followed by gas chromatography. The results indicate moderate toxicity to daphnia ([Bell, 1996).

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

One major use of the notified substance is an ingredient of domestic cleaning formulations. Most of the material will eventually be released into domestic sewerage systems as a consequence of product use.

The ecotoxicity data indicates that the notified substance is moderately toxic to daphnia. However, based on annual imports of 0.3 tonne, all presumed to be eventually released to sewer, daily nationwide release is estimated to be 0.82 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 0.3 µg/L. When released to receiving waters the concentration is taken to be reduced by a factor of 10, so the Predicted Environmental Concentration is around 0.03 µg/L. This is nearly five orders of magnitude less than the demonstrated acute toxicity to daphnia (EC_{50} = 1.5 mg/L).

The chemical is hydrophobic with log P_{ow} = 4.18. This indicates significant affinity for the organic component of soils and sediments, and is supported by the Simple Treat calculations that indicate that 44% would become bound to soils and sediments. Any residues in soil and sediments are expected to be slowly degraded to water, carbon dioxide and methane through biological processes. Such degradation would likely prevent bioaccumulation of the chemical.

Given the above, the notified substance is considered to pose minimal hazard to the environment when 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 has been used as a fragrance raw material for 10 years in the European Community, Japan and the USA. The notifier indicates that there are no reported cases of injuries or diseases during industrial use.

In support of the application, the notifier provided the following animal studies: acute oral, inhalation and dermal toxicity, skin and eye irritation and adjuvant and non-adjuvant skin sensitisation studies (Magnusson and Kligman Maximisation Test and Buehler Test, respectively). A non adjuvant skin sensitisation study was provided for Magnol (50% Magnol R in triethyl citrate) and an Ames test for investigation of mutagenicity. A repeat dose study was not provided.

The notified chemical was of very low acute oral toxicity (LD_{50} = 4 700 mg/kg) and low acute inhalation toxicity (LC_{50} >5.4 mg/L/4 hour). However, mortality occurred in the acute oral test and clinical signs suggestive of neurotoxicity were observed in both the oral and inhalation studies and it is noted that in 1994, the acute oral and inhalation studies were submitted by

Kao Corporation of America to the US EPA (under TSCA Section 8e) to report possible neurological effects which might result from over exposure to the notified chemical. Rats exhibited skin irritation, which persisted for 8 days, following topical application of the notified chemical in the acute dermal toxicity test (LD_{50} > 2 000 mg/kg). In rabbits, the notified chemical was a slight to moderate, although delayed, skin irritant and slight to moderate eye irritant. Magnol R was sensitising to guinea pig skin in both adjuvant and non adjuvant test methods (following challenge with 10 to 30% to the notified chemical). The formulation Magnol (diluted for challenge 2.5% of the notified chemical) was not considered a skin sensitiser in a non-adjuvant type test.

Mutagenic activity was observed in an initial test, but was not observed in repeat investigations using a range of dose levels and conditions. Because of the absence of mutagenic activity in follow-up studies, it was concluded the notified chemical did not exhibit mutagenic activity in the bacterial system tested. No other mutagenic data was provided.

The effects of the acute oral, inhalation and dermal studies in rats and the skin and eye irritation studies in rabbits are below the thresholds for classification of the notified chemical as a hazardous substance under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999). The notified chemical was not considered mutagenic in an Ames test. The notified chemical exhibited positive responses in both adjuvant and non adjuvant type tests for skin sensitisation. The percentage of animals showing evidence of delayed contact hypersensitivity in both studies met the criteria for classification as skin sensitiser. Therefore, the overall hazard classification for the notified chemical is Irritant (Xi) with risk phrase R43 – May Cause Sensitisation by Skin Contact.

Occupational Health and Safety

Exposure by inhalation and dermal routes is possible but no exposure data are available. Occupational exposure may occur during raw material testing and manipulation during formulation of the fragrance preparation (import concentration of 50% diluted to between 0.1% to 5%) and preparation of consumer products (maximum of 0.1%). Exposure via the lungs is likely to be low due to the low volatility of the notified chemical; the vapour pressure is 0.111 x 10^{-3} kPa at 25°C. The substance has a high octanol/water partition coefficient (Log P_{ow} = 4.1861 at 21°C) and the possibility of absorption through the skin cannot be excluded. However, the risk of acute health effects following dermal exposure is expected to be low given the low acute lethal dermal toxicity. In the absence of data on long term systemic effects, it is not possible to characterise the long term health risk in relation to repeated dose toxicity. The notified chemical is sensitising to guinea pig skin. In the absence of human repeat insult patch testing, there is moderate concern for the risk of skin sensitisation in susceptible workers. It is expected that the process in which the notified substance will be handled is non-dispersive, that is, the notifier indicates workers will receive site training in the safe-handling of chemicals. In addition, the notifier recommends that workers wear cuffed butyl rubber gloves, goggles, plastic face shields, aprons and boots and that local exhaust ventilation and splash proof filling devices should be used to prevent contact with the notified chemical. The engineering and personal protection controls are essential to control the risk of skin sensitisation.

Workers should be instructed to follow good hygiene practices and immediately remove contaminated clothing and any chemical that has come into contact with the skin with soap and water. Workers should be advised of the potential for occupational dermatoses following repeated skin exposure to Magnol-R and to report any skin changes to the occupational health and safety officer at their workplace. Further guidance on preventing the occurrence of occupational skin diseases can be found in the NOHSC guide *Occupational Diseases of the Skin* (NOHSC, 1990).

No significant risk of adverse effects is expected for workers using domestic products containing the notified chemical. The risk of adverse health effects to workers involved in transport and storage is considered to be negligible except in the case of accidental spillage.

Public Health
Members of the public will make dermal and inhalation contact, and possibly eye contact when using products containing the notified chemical. Although the notified chemical is a slight to moderate skin and eye irritant are not likely to occur because of the low concentration (approximately 0.1%) of the notified chemical in consumer products. While Magnol-R was a skin sensitiser in guinea pigs at 10%, the formulation Magnol was not a skin sensitiser in dilutions containing 2.5% of the notified substance. Based on the low concentration of the notified chemical in consumer products (approximately 0.1%) and the formulation in which the notified chemical will be present, skin sensitisation is not likely to occur. Therefore, it is considered that Magnol-R will not pose a significant hazard to public health when used in the proposed manner.

13. MATERIAL SAFETY DATA SHEET

The MSDS for Magnol-R and the product were provided in a format consistent with the *National Code of Practice for the Preparation of Material Safety Data* Sheets (NOHSC, 1994).

The 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.

14. RECOMMENDATIONS

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

- Workers to receive regular education and training on handling techniques, good hygiene practices and the potential for skin sensitisation from repeated contact with the notified chemical;

- The notifiers 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 of the potential for skin sensitisation;

- 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);

- Impermeable gloves should conform to AS/NZS 2161.2 (Standards Australia, 1998);

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

- Spillage of the notified chemical should be avoided. Spillage should be cleaned up promptly with absorbents which should then 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.

If the conditions of use are varied from the notified use (as a fragrance substance), greater exposure of the public may occur. In such circumstances, further information may be required to assess the hazards to public health.

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.

16. REFERENCES

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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