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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

2-cyclohexyl propanal

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Director
Chemicals Notification and Assessment

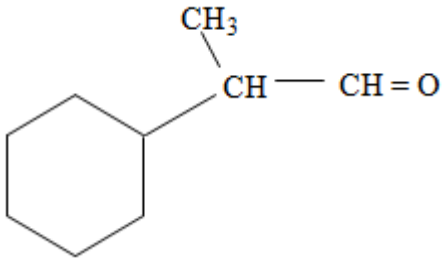
FULL PUBLIC REPORT

2-cyclohexyl propanal

1. APPLICANT

Kao (Australia) Marketing Pty Ltd of 103 Yerrick Road LAKEMBA NSW 2195 has submitted a standard notification statement in support of their application for an assessment certificate for 2-cyclohexyl propanal.

2. IDENTITY OF THE CHEMICAL

Chemical Name:	2-cyclohexyl propanal
Chemical Abstracts Service (CAS) Registry No.:	2109-22-00
Other Names:	Pollenal II
Trade Name:	Pollenal II
Molecular Formula:	$C_9H_{16}O$
Structural Formula:	
Molecular Weight:	140.2
Method of Detection and Determination:	ultraviolet-visible (UV/Vis), infrared (IR), nuclear magnetic resonance (NMR) and mass spectroscopy; gas liquid chromatography (GLC)

Spectral Data:	UV/Vis: the notified chemical in ethanol exhibited an absorbance peak at 220 nm IR: the 10 strongest peaks were 2 926, 2 853, 2 697, 1 725, 1 449, 1 399, 1 375, 1 001, 889 and 401 cm^{-1}; the peak at 2 926 was ascribed to CH, that at 2 697 to CH(C=O) and that at 1 725 to C=O NMR: ^{1}H-NMR was provided

Comments on Chemical Identity

The notified chemical is a well defined simple aldehyde containing a cyclohexyl moiety. The new chemical also contains up to 4% of unidentified impurities.

The notifier provided comprehensive spectroscopic data - IR, UV/Vis, NMR and mass spectroscopy - on the new chemical which may be used to identify the material. A GLC also accompanied the notification.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	clear colourless, non-viscous liquid
Boiling Point:	196.5-200.0°C at 1025 mbar
Specific Gravity:	0.915
Vapour Pressure:	0.0817 ± 0.0065 kPa at 25°C
Water Solubility:	423 mg/L at 20°C
Henry's Law Constant:	27.04 Pa/m^3/mole - see notes below.
Partition Co-efficient (n-octanol/water):	log P_{ow} = 2.95 at 20°C - see notes below
Hydrolysis as a Function of pH:	no significant hydrolysis at pH 4 and 7, some hydrolysis at pH 9 - see notes below.
Adsorption/Desorption:	log K_{oc} = 2.49 by QSAR calculations – see notes below
Dissociation Constant:	no data provided - see notes below
Surface Tension:	not surface active - see notes below.
Fat Solubility:	totally miscible - see notes below.

Flash Point: 91°C (closed cup)

Flammability: not flammable

Autoignition Temperature: 188°C

Explosive Properties: not explosive

Comments on Physico-Chemical Properties

Water solubility was determined by stirring an excess of the test substance with 100 mL of distilled water at 30 °C for 1, 2 and 3 days, equilibrating for 1 day 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. There was little difference between the results for those solutions prepared by stirring for 1, 2 or 3 days prior to equilibration (solubility at 20°C was determined as 432, 432 and 405 mg/L, respectively), which indicate that the reported solubility is reliable.

The Henry's Law constant was determined from the molecular weight, measured vapour pressure and water solubility using the equation-H= MW(g/mole) x Vapour Pressure (Pa)/Water solubility (g/L).

The degree of hydrolysis was determined at 50°C at pH 4, 7 and 9 over a 5 day test period. After 2.4 hours the degree of hydrolysis was respectively 0.7%, 1.8%, and 10.9%, and after 5 days 9.5%, 10.5% and 61.9%. Although hydrolysis is slow at pH 4 and 7, it is significantly higher at pH 9. However, the results indicate a half-life of between one day and one year for the chemical at 25°C and pH 9, and greater than one year at pH 4 and 7. Consequently the compound is not expected to exhibit significant hydrolysis under ambient environmental conditions.

The n-octanol/water partition coefficient was determined using the shake flask method, with analyses of both the aqueous and organic phases performed by gas chromatography. The determined value of Log P_{ow} indicates the new chemical has high affinity for hydrocarbon-like environments. Mass balance calculations on the quantities of new chemical partitioned into the n-octanol and water phases gave recoveries in excess of 96.8%, which indicates that the method used was appropriate for this determination, and the overall result is reliable.

Log K_{oc} was calculated from the value of Log P_{ow} using the relationship Log K_{oc} = 0.81 x Log P_{ow} + 0.10. This relationship is appropriate for predominantly hydrophobic compounds. The value for Log K_{oc} of 2.49 indicates that the chemical may partition into the organic component of soils and sediments, and become associated with these materials. However, this tendency may be reduced because of the high water solubility.

The compound contains no functionalities capable of readily dissociating in aqueous media. The notifier indicated that dissociation constant data were not applicable.

The new chemical is completely miscible in fat at 37°C (experimental report submitted), which is in accord with the predominantly hydrocarbon nature of the material and the high value for Log P_{ow}.

The material is marginally surface active, with the surface tension (Method 84/449/EEC (A5) of an aqueous solution containing approximately 90% of the test substance saturation of 60.6 mN/m at 20.5°C (water = 72.66 mN/m).

Calculations based on the molecular structure using the quantitative structure activity relationships (QSAR) of the US Environment Protection Agency ASTER database (reference 2) furnished the following estimates for environmentally relevant physico-chemical parameters. Where comparison with data supplied by the notifier is possible, the agreement is reasonable.

ASTER DATA (all calculated using QSAR)

Property	*QSAR estimate*
Boiling Point:	185°C
Vapour Pressure:	0.728 mm of Hg (90.05 Pa)
Water Solubility:	374 mg/L
Henry's Constant:	35.9 Pa/m^3/mole
log K_{ow}:	2.73
log K_{oc}:	2.82
Hydrolytic degradation half life:	hydrolysis is unlikely

4. PURITY OF THE CHEMICAL

Degree of Purity: 98.6% (range: 95.0 – 99.9%)

Toxic or Hazardous Impurities:

Chemical Name	*CAS No.*	*Weight %*
2-cyclohexyl propionic acid	not provided	< 1.0%
unknown		< 4.0%

Additives/Adjuvants:

Chemical Name	*CAS No.*	*Weight %*
2,6-ditertiary butyl 4-hydroxy toluene	128-37-0	< 0.05%

5. USE, VOLUME AND FORMULATION

The notified chemical is to be used as a fragrance enhancer in household, toiletry and

cosmetic products. It will be imported at a rate of 0.5 tonnes in the first year increasing to 1.7 tonnes/year by the year 2002.

The notified chemical will be imported in sealed, unbreakable lacquered steel drums of 32 or 200 L capacity mixed with other ingredients.

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

6. OCCUPATIONAL EXPOSURE

The notifier states that it will need only one waterside worker, forklift truck driver and truck driver to handle closed containers of the notified chemical. During transport or storage of drums containing the notified chemical occupational exposure may occur in the event of accidental spillage.

The chemical, in liquid form, is either manually or automatically charged to a mixer to be blended into a formulated perfume at a concentration of 0.1 – 5% which is then automatically filled into containers. The batch sizes were stated to be 25 kg, 50 kg, 100 kg, 500 kg or 1 tonne. The notifier states that quality control testing (sampling, analysis and odour evaluation) takes 2 to 3 minutes/day/person or one person a total of 6 to 9 minutes/day. Compounding (blending) which is either automated or manual, involves a single worker for 2 to 3 minutes/day. Discharge (filling of containers) is an automated process said to involve one worker for 5 minutes per day. During addition of the notified chemical to the mixer for production of the perfume formulation, exposure to spills is possible. Some exposure to the formulation could occur during quality control testing. The notifier states that cuffed butyl rubber gloves, goggles, plastic face shields, aprons and boots are worn during these processes. The notifier also states that there should be local exhaust ventilation in place and splash proof filling devices to prevent contact with the notified chemical. The mixing vessels are stated to retain 0.05% of the formulation (maximum 0.5 kg per batch) so that exposure to small amounts of the chemical during solvent washing is possible.

Exposure to spills is possible during addition of the perfume formulation to other ingredients followed by blending into household products and dispensing such products into containers. Local exhaust ventilation is in place over the mixing vessels. The perfume formulation is added to the mixing vessel either manually or automatically by a single worker. Filling of containers, such as cartons, plastic bottles, plastic film is an automatic or manual process. This is done at a number of customer sites although the details are not available. The perfume in incorporated into household products at approximately 0.1%.

7. PUBLIC EXPOSURE

The notified chemical will enter the public domain as household product (eg detergents, toiletries, cosmetics) containing the notified chemical at a low concentration (approximately 0.1%). Although the public will make dermal and inhalational contact, and possibly eye contact (eg. while using shampoos containing the notified chemical) with the notified chemical, exposure is likely to be negligible 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 use or from disposal is assessed as negligible.

8. ENVIRONMENTAL EXPOSURE

Release

The new product is used to prepare perfume blends, which are subsequently incorporated into soaps, detergents, fabric softeners and other household products, and may contain between 0.04 and 0.23% of the chemical. The notifier indicated that these production activities would be performed by a number of different companies. However, it is expected that production will take place in purpose constructed facilities, and the notifier made the following estimates in respect of 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 new chemical is lost through washing out the mixing vessels, and on an annual basis this amounts to a maximum loss of 0.85 kg. It was also stated that material released in the formulating plants as a result of equipment washing (and presumably any spillage) is sent with other waste to on-site treatment facilities which may include unit operations such as dissolved air flotation and granulated carbon filters. It is stated in the submission that 94% (annually around 0.80 kg) of the new chemical would be removed from the waste water by this treatment and become incorporated into the solid waste stream and incinerated. The treated waste water, containing the remaining 6% (annually around 50 g) of chemical is presumably discharged to the sewer systems.

It was indicated in the submission that no liquid waste streams are produced during production of the soap, detergent and other consumer products into which the perfume blend is added, but that around 0.01% of the new chemical (annually 170 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 160 g) would become incorporated in solid residuals and be incinerated.

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, this assessment estimates that 1% of total import quantity could be lost through accident, which amounts to an annual release of around 17 kg. If these spills are cleaned up with water and diverted to wastewater treatment at the manufacturing site where 94% of the chemical is removed and incinerated, an estimated 1.0 kg of chemical could be released from the manufacturing sites to sewage.

The notifier stated that the empty steel drums of the imported chemical would be sent for recycling. However, it is possible that the empty containers would be placed into landfill, and although no estimates of the amount of residual chemical left in the drums was presented in the application, this assessment estimates this at 0.05% of the import quantity, or around 0.85 kg per annum.

However, the new chemical is a fragrance enhancer for use in domestic cleaning products, and consequently all will be eventually released into the environment as a consequence of

normal product usage. It is expected that this release would be primarily to the sewerage system, although because of the measured vapour pressure of 81.7 Pa at 25 ^{o}C, much would be expected to volatilise and enter the atmosphere.

Empty containers of the consumer products are likely to contain some residual unused product; these packages would be discarded with domestic garbage and be disposed of to landfill.

Fate

The notifier provided a laboratory report on the assessment of the biodegradation of the notified chemical conducted in accordance with the OECD Test Guideline TG 301D (Closed Bottle Test). The results of this test indicated 11% loss of initial chemical oxygen demand (COD) of the test material after 28 days, and accordingly the notified chemical cannot be classed as readily biodegradable.

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 that a significant fraction would partition into the atmosphere. The Simple Treat Model (European Commission 1996 Part 2) may be used to estimate partitioning into different compartments, for the proportion of chemical which reaches the sewage treatment plant (ie is not volatilised or otherwise destroyed during passage to the plant). Based on a Henry's Law Constant of 27.04 Pa/m^3/mole, a Log K_{ow} of 2.95 and the compound not being biodegradable, the model indicates that the chemical is expected to partition into the air, water and sewer sludge compartments as follows -

AIR	WATER	SEWER PLANT SLUDGE
44%	50%	6%

Mackay Level 1 calculations from the ASTER database (US Environmetal Protection Agency 1998) indicate that when released to the environment the chemical would partition into the various compartments as listed below –

Atmospheric compartment	92.08%
Water compartment	7.31%
Soil compartment	0.31%
Aquatic biota compartment	0%

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 into the atmosphere or blown away by wind). Considering the assumptions and approximations inherent in both these models, particularly in respect of the significantly different Henry's Law Constant and partition coefficient used in each model, the difference between the two sets of results is not surprising. Both methodologies indicate significant partitioning to the 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 rapidly degraded through reaction with hydroxyl radicals (through hydrogen abstraction mechanisms). A calculation based on the methods described in OECD Environmental Monographs No 61 indicates that in the troposphere the new chemical would react with in this manner, with a rate constant estimated as 22.74 x 10^{-12} cm^3/molecule/sec. Rate constants of this order are indicative of fast degradation (OECD Environmental Monograph No 61), and the compound is not expected to persist in the atmosphere.

The new chemical is hydrophobic in character with Log P_{ow} =2.95, and estimated Log K_{oc} = 2.49. Consequently when released into the sewer system some would be expected to associate 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.

The residual chemical, which is disposed of to landfill within empty drums, discarded consumer packaging or with 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.

The ASTER calculations mentioned above also estimate a bioaccumulation factor of 58 for the compound in fish (fathead minnow). This is a low value for this parameter indicating little potential for bioaccumulation. Although the new chemical is hydrophobic, it is volatile and is consequently not expected to have prolonged residence times in the aquatic compartment or to bioaccumulate.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Summary of the acute toxicity of 2-cyclohexyl propanal

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} > 5 000 mg/kg for males LD_{50} > 2 000 mg/kg for females	(Allan, 1992a)
acute dermal toxicity	rat	LD_{50} > 2 000 mg/kg	(Allan, 1992b)
acute inhalation toxicity	rat	LC_{50} > 5.32 mg/L	(Jackson, 1994)
skin irritation	rabbit	slight to moderate irritant	(Liggett, 1992a)

eye irritation	rabbit	slight irritant	(Liggett, 1992b)
skin sensitisation	guinea pig	sensitiser	(Parcell, 1992)

9.1.1 Oral Toxicity (Allan, 1992a)

Species/strain:	rat/Sprague-Dawley
Number/sex of animals:	5/sex (group 1) 5 females (group 2)
Dose:	5 000 mg/kg (group 1) 2 000 mg/kg (group 2)
Observation period:	14 days
Method of administration:	gavage
Clinical observations:	piloerection was observed in all rats and increased salivation in rats treated with 5 000mg/kg within five minutes of dosing; after day 1 abnormal gait was observed in all rats; hunched posture, lethargy, decreased respiratory rate, ptosis and pallor of the extermities were observed in rats dosed with 5 000 mg/kg; prostration was observed in one dead female; recovery of rats, as judged by external appearance and behaviour, was complete: by day 2 for rats dosed with 2 000 mg/kg; by day 3 for all but one rat dosed at 5 000 mg/kg; and day 4 for one female dosed at 5 000 mg/kg; body weight gain was not affected by treatment
Mortality:	2 females from group 1
Morphological findings:	none
Test method:	Directive 84/449/EEC (OJ No. L251) Part B Method B.1 (European Economic Community, 1984)
LD_{50}:	> 5 000 mg/kg for males > 2 000 mg/kg for females
Result:	the notified chemical was of very low acute oral toxicity in rats

9.1.2 Dermal Toxicity (Allan, 1992b)

Species/strain:	rat/Sprague-Dawley

Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	the notified chemical, a viscous liquid, was spread evenly over an area of approximately 25 cm^2 and covered with an occlusive dressing for 24 hours
Clinical observations:	no signs of systemic reaction to treatment; well defined erythema in nine rats, slight erythema in one rat and slight oedema in male rats were observed on day 2; all animals recovered by day 5
Mortality:	none
Morphological findings:	none
Test method:	Directive 84/449/EEC (OJ No. L251) Part B Method B.3 (European Economic Community, 1984)
LD_{50}:	> 2 000 mg/kg
Result:	the notified chemical was of low acute dermal toxicity in rats

9.1.3 Inhalation Toxicity (Jackson, 1994)

Species/strain:	rat/Sprague-Dawley
Number/sex of animals:	5/sex (test and control groups)
Observation period:	14 days
Dose(Exposure Concentration)	5.32 mg/L
Method of administration:	snout only exposure to (liquid) aerosol (87% within respirable range) for 4 hours
Clinical observations:	a soiled appearance of the fur was noted on day 0 for test and control animals; exaggerated respiratory movements, staggering gait and poor grooming noted up to day 3; brown staining around the snout, jaws and around the eyes were persistent after day 3; food consumption of the test group slightly reduced on day 1
Mortality:	none

Morphological findings: none

Test method: OECD guideline TG 403 (Organisation for Economic Co-operation and Development, 1995-1996)

LC_{50}: > 5.32 mg/L

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

9.1.4 Skin Irritation (Liggett, 1992a)

Species/strain: rabbit/New Zealand White

Number/sex of animals: 3/females

Observation period: 12 days

Method of administration: 0.5 mL of the notified chemical applied under a 625 mm^2 gauze pad under occlusive dressing for 4 hours

Draize scores:(Draize, 1959) of unirrigated eyes

Animal #	***Time after treatment (days)***									
	*******	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***
Erythema										
1	1	1	2	2	2	2	2	1a	0a	0a
2	1	1	2	2	2	2	2a	1a	0a	0a
3	1	1	2	2	2	2	2a	1a	1a	0a
Oedema										
1	1	1	1	1	1	1	1	1	0	0
2	1	1	2	2	2	2	1	1	0	0
3	1	1	2	2	2	2	1	1	1	0

see Attachment 1 for Draize scales a=sloughing of epidermis *=approximately 30 minutes after removal of the dressing

Test method: Directive 84/449/EEC (OJ No. L251) Part B Method B.4 (European Economic Community, 1984)

Result: very slight erythema was observed in all three animals 30 minutes after removal of the dressing; well-defined erythema was seen in all three animals from day 2 to 6 and continued as very slight erythema up to day 7 and in one animal up to day

8; very slight oedema was observed in all three animals 30 minutes after removal of the dressing which persisted up to day 7 in one animal; slight oedema was observed in two animals from day 2 to 5 and continued as very slight oedema up to day 7 and day 8 (one animal); desquamation of the *stratum corneum* (sloughing) was seen in 2 animals from day 6 and in all three animals from day 7 to day 10

the notified chemical was a moderate skin irritant in rabbits

9.1.5 Eye Irritation (Liggett, 1992b)

Species/strain:	rabbit/New Zealand White
Number/sex of animals:	one male and two females
Observation period:	7 days
Method of administration:	0.1 mL of the notified chemical into the conjunctival sac of one eye
Test method:	Directive 84/449/EEC (OJ No. L251) Part B Method B.5 (European Economic Community, 1984)
Result:	dulling of the cornea was observed in 2 animals one hour after instillation; scattered and diffuse areas of corneal opacity was observed in 2 animals on day 1 and persisted up to day 3 in one animal; no iridal effects were observed; all rabbits exhibited mild to moderate redness and chemosis of the conjunctiva 1 hr post-instillation which persisted to day 1 or 2; no other effects were seen up to 7 days post-instillation the notified chemical was slight eye irritant in rabbits

9.1.6 Skin Sensitisation (Parcell, 1992)

Species/strain:	guinea pig/Dunkin-Hartley
Number of animals:	20 test; 10 controls
Induction procedure:	3 pairs of intradermal injections in the scapular region as follows:

- Freund's Complete Adjuvant (FCA) diluted 1:1 with water;
- notified chemical, 10% (v/v) in Alembicol D
- notified chemical, 10% (v/v) in FCA and Alembicol D 1:1

seven days after the above treatment, topical induction was performed by applying a 8 cm^2 filter paper soaked with 0.4 mL of the notified chemical to the same scapular region under occlusive dressing for 48 hours; control animals were similarly treated but without the notified chemical

Challenge procedure:

14 days after topical induction, test and control animals were challenged using notified chemical, at 75% and 40% (v/v) in Alembicol D

anterior site on the flank of each test animal was treated with 0.2 mL of the notified chemical, 75% (v/v) in Alembicol D and the posterior site was treated with 0.2 mL of the notified chemical, 40% (v/v) solution in Alembicol D under occlusive dressing for 24 hours; control animals were similarly treated but without the notified chemical

Challenge outcome:

	Test animals		***Control animals***	
Challenge concentration	***24 hours****	***48 hours****	***24 hours***	***48 hours***
75% (v/v) in Alembicol	**20/20	20/20	0/10	0/10
40% (v/v) in Alembicol	20/20	19/20	0/10	0/10

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

Challenge outcome:

marked persistent erythema and oedema were observed in all test animal on the challenge sites at 24 and 48 hours after patch removal

Test method:

Directive 84/449/EEC (OJ No. L251) Part B Method B.6 (European Economic Community, 1984)

Result:

the notified chemical was a skin sensitiser in

guinea pigs

9.2 Repeated Dose Toxicity (Edwards, 1992)

Species/strain:	rat/Sprague-Dawley Crl:CD (SD)
Number/sex of animals:	5/sex/group
Method of administration:	the notified chemical in corn oil was administered by gavage
Dose/Study duration::	control: 0 mg/kg/day for 28 days low dose: 15 ″ ″ mid dose: 150 ″ ″ high dose: 1 000 ″ ″
Water consumption:	a relative increase in water consumption was observed in high dose group males (12.6%) and females (24.5%); at lower dose groups this effect was not remarkable
Clinical observations:	occasional salivation (with greater frequency in males) in mid dose rats; salivation in high dose rats was persistent from day 2; waddling gait was observed in high dose rats accompanied by a slight lethargy; occasional pilo-erection and thin appearance observed in high dose females
Clinical chemistry/Haematology	*clinical chemistry:* statistically significant increases in globulin levels accompanied by an increase in total protein levels in males; a decrease in glutamic oxaloacetic transaminase (GOT) in high dose group; relative increase in glucose in high dose females; all the above changes in comparison to historical range was considered to be incidental; at high dose a decrease in chloride ($p<0.01$) in both male and females, which in females, was accompanied by increased phosphorous ions; two (2/5) individual chloride ion values among females and one (1/5) among males were slightly below the background range and may indicate treatment related effects

	haematology: statistically significant increase in thrombotest time and variation in mean cell volume were observed in high dose males but were not dose dependent; decreased eosinophil levels observed in high dose females were within the historical range
Body/Organ weights:	statistically significant reduction in mean bodyweight gain in high dose males; in females a statistically increase was observed at week 2 only; significantly lower absolute spleen weights observed in high dose males and significantly increased absolute and relative kidney weights observed in high dose females; it was argued that the majority of individual values were within the historical background range
Macroscopic findings:	small prostates and minimal contents in seminal vesicles in high dose males
Histopathology:	focal tubular basophilia and/or cortical scarring of the kidney is the high dose group were considered background events
Test method:	Directive 84/449/EEC (OJ No. L251) Part B Method B.7 (European Economic Community, 1984)
Result:	the target organ was identified as the blood, with changes judged to be of minor importance and adaptive in nature; the no observable effect level (NOEL) was judged to be 15 mg/kg/day on the basis of salivation in rats at mid and high dose.

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* Reverse Mutation Assay (Jones & Kitching, 1992)

Strains:	TA 1535, TA 1537, TA 1538, TA 98 and TA 100
Concentration range:	0, 1.5, 5, 15, 50 and 150 μg/plate
Test method:	OECD guideline TG 471 (Organisation for Economic Co-operation and Development, 1995-1996)

Result:	toxicity of the notified chemical was noted at 500 and 5 000 µg/plate so the top dose in the main test was reduced to 150 µg/plate; no increase in the number of prototrophic (histidine-independent) back mutants was observed up to the top dose in the presence or absence of metabolic activation provided by Aroclor-induced rat liver microsomal preparations (S9 fraction); negative and positive controls gave the expected responses.

9.3.2 Chromosomal Aberrations in Human Lympocytes *in vitro* (Jones et al., 1992)

Cells:	lymphocytes from healthy human male donors, stimulated to divide with phytohaemagglutinin (PHA)
Treatment regime:	Aroclor 1254-induced rat liver microsomal preparations (S9 fraction) were added to cultures treated for 16 hours with 0, 78.1, 321.5 and 425 µg/mL or for 24 hours with 0, 19.5, 312.5, 625 and 5 000 µg/mL of the notified chemical; cultures without S9 fraction were treated at 0, 39.1, 156.3 or 312.5 µg/mL for 16 hours; 100 cells were examined per dose level
Test method:	OECD guideline TG 473 (Organisation for Economic Co-operation and Development, 1995-1996)
Result:	no increase in the number of chromosomal aberrations (either including or excluding gaps) occurred in cultures treated for 16 hours (with or without S9 fraction) with the notified chemical relative to controls; there was a statistically significant and reproducable increase in the number chromosomal aberrations in cultures treated at 625 µg/ml for 24 hours in the presence of S9 mix; in a repeat test of 625 µg/ml to 5 000 µg/ml, there was a statistically significant increase in aberrant cells at all doses; positive and negative controls gave the expected responses the notified chemical was clastogenic in human lymphocytes in the presence of S9 mix

9.3.3 Micronucleus Assay in the Bone Marrow Cells of the Mouse (Proudlock, 1992)

Species/strain:	mice/CD-1

Number and sex of animals:	40/sex; 3 groups
Doses:	1 920 mg/kg; mitomycin C (12 mg/kg) as positive control and aqueous 1% methylcellulose as negative control
Method of administration:	intragastric gavage;
Test method:	similar to OECD guidelines 474 and EEC annex V committee No. L 251B
Result:	no reduction in the ratio of polychromatic erythrocytes or significant increase in polychromatic erythrocytes were observed at any dose level when observed at 24, 48 and 72 hour time points the notified chemical has not shown any evidence of causing chromosome damage

9.4 Overall Assessment of Toxicological Data

The notified chemical was of very low acute oral toxicity (males) and inhalation toxicity (LD_{50} > 5 000 mg/kg for oral toxicity; LC_{50} > 5.32 mg/L for inhalation toxicity) and of low acute oral toxicity (females) and dermal toxicity (LD_{50} > 2 000 mg/kg) in rats. It was a slight to moderate skin irritant and a slight eye irritant in rabbits. It was a skin sensitiser in guinea pigs.

Clinical signs of persistent salivation were observed in a 28-day oral repeat dose study in rats at mid and high doses. The NOEL was 15 mg/kg/day.

The notified chemical was clastogenic in human lymphocytes in the presence of S-9 mix but was not mutagenic in bacteria *in vitro* or *in vivo* in the mouse micronucleus assay. Based on these test results the notified chemical is considered to be weakly genotoxic.

The notified chemical would be determined to be a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* in terms of skin sensitisation and persistent skin irritation (National Occupational Health and Safety Commission, 1994a).

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.

Test	Species	Results (Measured)
Acute Toxicity [OECD 203]	*Oncorhynchus mykiss* (Rainbow trout)	LC_{50}(96 h) = 3.2 mg/L NOEC (96 h) = 1.5 mg/L
Acute Immobilisation [OECD 202 Part 1]	*Daphnia magna*	EC_{50}(48 h) = 1.2 mg/L NOEC(48 h) = 0.6 mg/L

The tests on rainbow trout were performed using solutions of the test material made up in dechlorinated water. Stock solutions of the test were automatically dispensed into the 20 L test vessels at a rate of 0.35 mL/h, while the medium itself was continuously renewed at approximately 118 mL/min. The tests were conducted over a 96 hour period at a controlled temperature of 14°C. Five solutions of the chemical with mean measured concentrations of 0.8, 1.5, 2.8, 4.8 and 9.0 mg/L were tested, together with one control. Solution analysis was conducted by extraction with dichloromethane followed by gas chromatographic determination of the extracted test chemical on water samples taken at 0, 24 and 96 hours after commencement of the tests. The measured results were (with one exception) always within 25% of the nominal concentrations.

Ten fish were tested at each concentration, and during these tests the pH of the test solutions was always between 7.1 and 7.2, while dissolved oxygen concentrations (DOC) were always between 10.1 and 10.3 mg/L.

The tests results indicate that the notified chemical is moderately toxic to the rainbow trout with a 96 hour LC_{50} of 3.2 mg/L determined using the method of Thompson and Weil (1952). The responses listed in the raw data were such that Probit analysis was not possible, but this assessment places the 96 hour LC_{50} between 2.8 and 4.8 mg/L.

The acute immobilisation tests on daphnia were performed using solutions of the test material made up in dechlorinated water. A stock solution of the test material (containing Tween 80 detergent and acetone to assist solubility) was serially diluted and used in a static non renewal system over a 48 hour period at a controlled temperature of 21°C. Nine solutions of the chemical with nominal concentrations of 0.32, 0.58, 1.0, 1.8, 3.2, 5.8, 10, 18 and 32 mg/L were tested, together with one control. Solution analysis was conducted on medium samples taken at 0 and 48 hours, by extraction with dichloromethane followed by gas chromatographic determination of the extracted test chemical. The relevant measured concentrations were 0.6, 2.1, 4.4 and 7.6 mg/L.

Ten daphnia were tested in duplicate at each concentration. During these tests the pH of the test solutions was always between 7.1 and 7.2, while DOC levels (measured for the control only) were always between 8.0 and 8.9 mg/L. The criterion for deciding on immobilisation was if the animals were unable to swim after gentle agitation of the test vessel. The tests results indicate that the notified chemical is moderately toxic to daphnia with a 48 hour EC_{50} of 1.2 mg/L determined using the method of Thompson and Weil (1952). The responses listed in the raw data were such that Probit analysis was not possible, but this assessment places the 48 hour EC_{50} between 0.6 and 2.1 mg/L.

The notifier did not provide laboratory reports on the effect of the chemical on daphnia reproduction or algal growth, since these studies had not been conducted. However, this deficiency was acknowledged and some calculated estimates comparing the Predicted

Environmental Concentration (worst case scenario) with Predicted No Effect Concentration (taken as 1/1000 of the daphnia EC_{50}) were presented.

The QASR calculations of the ASTER database (US Environmetal Protection Agency 1998) also furnished a predicted LC_{50} = 8.7 mg/L for acute toxicity to Fathead minnow.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The majority of the new chemical is an ingredient of domestic cleaning products and most of the material would eventually be released into domestic sewerage systems as a consequence of product use. However, due to the volatility of the material, a high proportion is expected to enter the atmosphere.

The ecotoxicity data indicates that the new chemical is moderately toxic to the aquatic test species. However, based on maximum estimated annual imports of 1.7 tonne, all of which is eventually released to sewer, the daily release on a nationwide basis is 8.2 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 1.7 µg/L. When released to receiving waters the concentration is generally understood to be reduced by a further factor of at least 10, so the Predicted Environmental Concentration is around 0.17 µg/L. This is nearly four orders of magnitude less than the demonstrated chronic toxicity to the daphnia (EC_{50} = 1.2 mg/L), the most sensitive species against which the new chemical was tested.

The chemical is hydrophobic with Log P_{ow} = 2.95, indicating significant affinity for the organic component of soils and sediments. The Simple Treat and Mackay Level 1 calculations mentioned above 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 hydroxy free radicals. Nevertheless, it is likely that some of the chemical would become bound to soils and sediments, and here is 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 aqueous compartment, so overall environmental concentrations would be unlikely to increase with prolonged release of the chemical.

The above considerations indicate minimal hazard to the environment when the new chemical is used as a component of domestic products in the manner indicated by the notifier. However, it should be appreciated that the new compound will be used in perfume formulations with two similar chemicals (NICNAS submissions NA/633 and NA/634), which will be present in the products at similar levels. Consequently the safety margin for environmental hazard will be reduced by a factor of approximately 10. Algae and chronic daphnia tests are only available for the chemical addressed in the report on NA/634, where the chronic test shows that chemical NA/634 is less toxic than the acute result for either the present chemical or NA/633.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

On the basis of the submitted toxicological data the notified chemical is unlikely to exhibit acute or subacute systemic toxicity. However, it may be a slight to moderate skin irritant and slight eye irritant. It is a strong skin sensitiser and is weakly genotoxic. The notified chemical would be classified as hazardous according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* in terms of skin sensitisation and persistent skin irritation. It would warrant the risk phrases R38 Irritating to skin and R43 May cause sensitisation by skin contact. The number and type of genotoxic studies conducted are insufficient to consider a hazardous substances classification for genetic effects.

The risk of adverse health effects to workers involved in transport and storage is considered to be minimal except in the case of accidental spillage, where there may be a slight risk of eye or skin irritation and a strong chance of skin sensitisation if exposure is repeated. There is a risk of eye or skin irritancy or skin sensitisation during manual addition of the notified chemical to vessels used for formulating perfume for household products, during sampling for quality control purposes and during system maintenance. The risk of these effects is likely to be highest during handling of the undiluted chemical for example when adding to mixing vessels. The risk of irritation is much reduced, but the real possibility of skin sensitisation (and respiratory sensitisation) remains for workers handling the formulated perfume. The notifier states that the concentration of the chemical in the formulated perfume is up to 5%, which would be a hazardous substance based on skin sensitisation, where the cut off concentration is ≥ 1%. The risk of eye or skin irritation during automatic packaging is likely to be negligible however, given that the material is a strong sensitiser sensitising reactions may develop if the exposure to the chemical occurs. The notifier states that workers will use organic solvent resistant gloves, such as butyl rubber gloves, and safety glasses; processes will occur under local exhaust ventilation. It is critical that all feasible steps are taken to reduce dermal and inhalation exposure to the notified chemical.

There is a slight risk of eye or skin irritation and a real risk of sensitisation for workers involved in manual addition of the perfume formulation to vessels used to blend household products. Once the end use products are mixed, the risk of irritation and sensitisation resulting from exposure to the notified chemical is very low as it is present in very small amounts (0.1%).

Workers conducting quality control testing, machine maintenance and package filling will be at an equivalent risk and need to take precautions to avoid contamination with the chemical.

Given the strong sensitising effects seen in experimental animals, this assessment recommends that workers who have become sensitised should not continue to handle the chemical in the workplace.

Although members of the public will make dermal and inhalational contact and possible eye contact with the notified chemical, exposure is likely to be negligible because of the low concentration of the notified chemical in consumer products (approximately 0.1%). Although the notified chemical is a slight to moderate skin irritant, a slight eye irritant, a skin sensitiser and is weakly genotoxic, these hazards are unlikely to be significant because of the low concentration of the notified chemical in the products.

13. MATERIAL SAFETY DATA SHEET

The MSDS for the notified chemical was provided in accordance 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.

14. RECOMMENDATIONS

To minimise occupational exposure to the notified chemical 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);
- 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. 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.
- Sensitised workers should not continue to handle the chemical in the workplace.
- The notified chemical may be recommended to the National Occupational Health and Safety Commission for consideration for inclusion in the NOHSC List of Designated Hazardous Substances.

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. Also, if annual imports of the new material exceed 7 tonnes (four times the present estimates), we will require full test results and reports on the effects of the chemical on *daphnia* reproduction and the inhibition of algal growth.

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