File No: NA/753

23 April 2020

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

2,4,4,7-tetramethyl-6-octen-3-one (Claritone)

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

2,4,4,7-tetramethyl-6-octen-3-one (Claritone)

1. APPLICANT

Haarmann & Reimer (Australia) Pty Ltd of 9 Garlings Road KINGS PARK NSW 2148 has submitted a limited notification statement in support of their application for an assessment certificate for 2,4,4,7-tetramethyl-6-octen-3-one.

2. IDENTITY OF THE CHEMICAL

The notifier has not claimed any information to be exempt from publication in the Full Public Report.

Chemical Name: 2,4,4,7-tetramethyl-6-octen-3-one

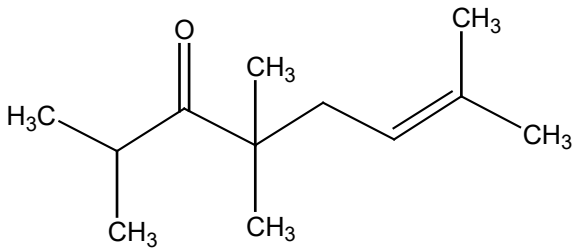
Chemical Abstracts Service (CAS) Registry No.: 74338-72-0

Other Names: HR 97/600285; HR 96/917449; HR 94/020670

Marketing Name: Claritone

Molecular Formula: $C_{12}H_{22}O$

Structural Formula:



Molecular Weight:	182
Method of Detection and Determination:	infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy
Spectral Data:	characteristic peaks were found in the IR spectrum at: 2 962, 2 933, 1 703, 1 471, 1 381, 1 177, 1 090, 1 039, 851 and 780 cm^{-1}

Comments on Chemical Identity

The notified chemical is a small ketone which contains a single unsaturated function. The notifier provided comprehensive spectroscopic data on the new chemical which serves to identify the material. In the Gas Chromatogram (GC) trace that accompanied the notification, the area under the major peak was very sharp and well defined, indicating that the major component of the material comprised over 96% of the sample.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	colourless clear liquid
Freezing point:	between -52 and -46°C
Boiling Point:	184°C at 101.3 kPa
Density:	830 kg/m^3 at 20°C
Vapour Pressure:	2.2×10^{-2} kPa at 25°C
Water Solubility:	59.1 ± 2.1 mg/L at 20°C
Henry's Law Constant:	67 Pa/m^3/mole
Partition Co-efficient (n-octanol/water):	Log P_{ow} = 4.5 at 20°C
Hydrolysis as a Function of pH:	$T_{1/2}$ at 25°C > 1 year at pH 4.0, 7.0 and 9.0
Adsorption/Desorption:	not provided
Dissociation Constant:	not provided
Flash Point:	83°C

Flammability Limits:	not flammable
Degradation Products:	Thermal degradation to water and oxides of carbon
Autoignition Temperature:	255°C
Explosive Properties:	not explosive
Particle size:	not applicable
Reactivity/Stability:	not reactive under normal conditions of use

Comments on Physico-Chemical Properties

Vapour pressure was determined at a number of temperatures between 85°C and 210°C and the data was fitted to the general Antoine equation:

P (vapour pressure in Pa) = $10^{(7.1625-1678.4/(T+189.7))}$, where T is the temperature in °C.

Water solubility was determined using the flask method whereby a saturated solution of the test substance is prepared by stirring an excess of the test chemical with distilled water for around 24 hours at a temperature in excess of 20°C. The flasks are then allowed to equilibrate to 20°C, and the excess solute removed through filtration or centrifugation. The concentration of the test material dissolved in the aqueous phase is then determined through High Performance Liquid Chromatography (HPLC). Fifteen individual determinations provided the water solubility result tabulated above.

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/m^3).

The rate of hydrolytic degradation of aqueous solutions containing measured concentrations of the test material (16.9–20.2 mg/L) were determined at pH 4.7 and 9.0 at 50°C over a five day test period. Samples were analysed for the non degraded compound at three different times after commencement of the tests (approximately 24 h, 48 h and 120 h) using HPLC. The percentage loss was used to derive the half lives listed above assuming pseudo first order kinetics. These data are interpreted to indicate a half life of greater than one year at 25°C in the environmental pH range.

The n-octanol/water partition coefficient was determined by HPLC, where the retention time of the test compound on C_{18} columns was compared with eight reference compounds of known K_{ow}. The reference range for Log K_{ow} was 1.6 (benzonitrile) to 6.6 (2,4-DDT). The relatively high value for Log K_{ow}, determined as 4.5 indicates the new chemical has appreciable affinity for hydrocarbon like environments.

No data for Log K_{oc} was provided in the dossier, but it is possible to estimate this parameter from the value of Log P_{ow} using quantitative structure activity relationships (QSARs). The EEC (EC, 1996a) give a number of equations for this purpose, including one which is appropriate for chemicals which are predominantly hydrocarbon in nature:

$\text{Log } K_{oc} = 0.81 \text{ X Log } K_{ow} + 0.1$

and estimates 3.7 for this quantity. The calculated value for Log K_{oc} as 3.7 indicates that the chemical has a large tendency to partition into the organic component of soils and sediments and is likely to become associated with these materials. However, the moderately high water solubility indicates that the compound may be also exhibit some mobility in the soil compartment.

The compound contains no functionality capable of dissociating or otherwise becoming ionised in aqueous media, and dissociation constant data are not applicable.

Calculations based on the molecular structure using QSARs of the US Environment Protection Agency ASTER database (USEPA, 1998) gave the following estimates for environmentally relevant physico-chemical parameters. Where comparison with data supplied by the notifier is possible, the agreement is reasonable except for the estimate of vapour pressure and the derived value of the Henry's Law constant which are significantly lower than the corresponding data listed above.

ASTER DATA (all calculated using QSARs)

PROPERTY	***QSAR ESTIMATE***
Boiling Point	240ºC
Vapour Pressure	0.0095 mm of Hg (1.24 Pa)
Water Solubility	80.7 mg/L
Henry's Law Constant	2.8 Pa/m^3/mole
Log K_{ow}	3.37
Log K_{oc}	3.17
Hydrolysis	hydrolytic degradation not considered likely

4. PURITY OF THE CHEMICAL

Degree of Purity: 96.7%

Hazardous Impurities: none

Non-hazardous Impurities (> 1% by weight): none

5. USE, VOLUME AND FORMULATION

The notified chemical will not be manufactured in Australia. It will be imported and used as an odourant in fragrance compounds. The fragrance compounds contain 0.01% to 10% of the notified chemical (typically 1%). Claritone-containing fragrance compounds will be used in the formulation of shampoos and fabric care goods such as fabric conditioners and pre-wash sprays. The concentration of Claritone in consumer products is 0.00001% to 2%, typically 0.01%.

It is estimated that not more than 200 kg of the notified chemical will be imported per annum in the first five years.

6. OCCUPATIONAL EXPOSURE

The notified chemical will be imported in 30 L lacquered aluminium containers. It will be transported by road from the docks to the notifier's warehouse stored in its original air-tight packaging.

Transport and Storage
Worker exposure is not expected during transport and storage except in the event of an accident.

Quality Control
On receipt into storage, 1-2 workers will sample the notified chemical. Sampling involves random extraction of 25 g of the liquid, quality observation and storage of the extract for reference. The frequency and duration of sampling and protective clothing used during sampling were not provided. The notifier does not anticipate significant worker exposure as a result of quality control activities.

Mixing
The notifier states that mixing will take place at a single mixing site, where the notified chemical will be mixed with other raw materials to produce a fragrance compound. Mixing is typically a batch process conducted in small volumes. It involves decanting 250 – 500 g of the notified chemical from the drum, weighing and mixing it with other raw materials in an isolated blending room. Although details of the mixing process were not provided, it is possible that mixing may be an open process. On completion, the fragrance compound is

packed in 60 kg drums for delivery to customers. The notifier did not provide details on the packaging process.

The predominant routes of exposure during mixing are dermal and ocular. Inhalation exposure is not expected to be significant due to the low vapour pressure of the liquid. The notifier recommends the use of chemical resistant (PVC) gloves to minimise skin contamination. The mixing site is equipped with exhaust ventilation.

Mixing will be conducted by 5-6 workers, once per day, 5 days per week, depending on customer demand. The duration of exposure is expected to be 2- 21/2 hours per batch.

Incorporation
The fragrance compound is incorporated into a range of shampoos and fabric care products at several sites across Australia. The notifier indicates that worker exposure will be limited due to the entrapment of the fragrance compound within the plant. Packaging is an automated process, further limiting potential worker exposure.

7. PUBLIC EXPOSURE

Public exposure is expected to be negligible from transport, storage, mixing into fragrance compounds, incorporation into consumer products and disposal. Accidental spills will be taken up with absorbent materials and disposed of by incineration as recommended in the Material Safety Data Sheet (MSDS).

Although members of the public will make dermal, inhalation and possibly ocular contact with the notified chemical, exposure is expected to be negligible due to the low concentration of the chemical in consumer products (maximum concentration 2%, typical concentration 0.01%).

8. ENVIRONMENTAL EXPOSURE

Release

The notifier indicated formulation of the fragrances and use of the fragrances in manufacture of the final products would take place at a number of different sites. It is expected that all production activities will take place in purpose constructed facilities.

The notifier indicates that around 1% of the new chemical (annually 2 kg) may be lost as a consequence of cleaning the blending and filling equipment, and discharged to the sewer system. Assuming production takes place for 200 days each year, this equates to a daily release of 25 grams. No reference to the quantities of chemical likely to be lost and released as results of accidental spillage was made in the submission. However, it is estimated that a further 1% of total import quantity could be lost accidentally, corresponding to 2 kg annually, some of which is expected to be washed into the sewer system.

The notifier indicated that the amount of residual chemical left in the containers and drums could be 0.5 % of the import quantity, or around 1.0 kg per annum. These residues would be disposed of to landfill with the empty containers. Consequently around 5 kg of the imported

chemical is estimated to be released annually as a consequence of formulating and manufacturing activities, with most discharged to the sewer system.

As the new chemical is a fragrance for use in domestic cleaning and personal care products, all will eventually be released into the environment as a result of normal product usage. It is expected that a high proportion of the chemical would be released into the sewage system, although due to the moderate vapour pressure some would be expected to volatilise and be directly released to the atmosphere.

Empty containers of the consumer products are likely to contain some residual unused product, and these packages would be discarded with domestic garbage and be disposed of into landfill. However, this release could be expected to be uniform across the nation, and consequently very diffuse, and at low levels.

Fate

Models
All of the new chemical will eventually be released into the environment and the majority is expected to be discharged into sewer systems. However, once released in this manner the moderately high vapour pressure indicates some partitioning into the atmospheric compartment. For that proportion of the chemical which reaches sewage treatment plants (i.e. is not volatilised or otherwise destroyed during passage to the plant), it is possible to estimate the equilibrium partitioning of the chemical from the SimpleTreat Model (EC, 1996b). These estimates are based on the chemical having a calculated Henry's Law constant of 67 $Pa/m^3/mole$, a Log K_{ow} = 4.5 (experimentally determined) and not being biodegradable (see below). The model indicates that the chemical could be expected to partition into the air, water and sewer sludge compartments as follows

Air	***Water***	***Sewer Plant Sludge***
~20%	~25%	~55%

The calculated estimates of vapour pressure and Henry's Law constant from the ASTER database (USEPA, 1998) are lower than the experimental data, and Mackay Level 1 calculations based on the calculated data also indicate significant partitioning of the compound to water. The Mackay model also assumes equilibrium is established between all phases, and the partitioning into the various environmental compartments resulting from this model is:

Atmospheric compartment	42.1 %
Soil compartment	7.9 %
Sediment compartment	7.38 %
Water compartment	42.63 %
Aquatic biota compartment	0.00%

However, in the environment an equilibrium state will not be reached as chemical which reaches the atmosphere will be effectively removed from the system by diffusion and degradation through reaction with hydroxyl radicals (see further below). This mechanism will continuously remove the compound from the water compartment.

Biodegradation
The notifier provided a laboratory report on the assessment of the biodegradation of Claritone conducted in accordance with the OECD Test Guideline TG 301D (Closed Bottle Test). The results of this test were variable and inconclusive, but indicated only slight biodegradation. It was indicated that preferential dissolution of some of the impurities present in the chemical may have been responsible for the variations. However, the volatility of the compound may have contributed to the variations.

The notifier also provided a laboratory report on the assessment of the biodegradation of the chemical conducted in accordance with the OECD Test Guideline TG 301F (Manometric Respirometry Test). The results of this test indicated 8 % degradation of the test material (as estimated from the decrease in the Chemical Oxygen Demand) after 28 days, while the reference substance aniline was 84% degraded after 28 days. Accordingly, the compound Claritone cannot be classed as readily biodegradable.

Atmosphere
Once released to the atmosphere the chemical would be quickly decomposed through photolytically promoted free radical reactions. Hence, over time the sediment/water and water/air partitioning will be driven toward the loss of the chemical to the atmosphere. In the atmosphere, it is likely that the substance will be degraded through reaction with hydroxyl radicals, primarily through hydroxyl addition to the molecule alkene functionality. A calculation based on the methods described in OECD (1992a) indicates that the new chemical would react this way in the troposphere with an estimated rate constant of 87 x 10^{-12} cm^3/molecule/sec. The corresponding rate constant for hydrogen abstraction is around 4 x 10^{-12} cm^3/molecule/sec, giving a combined rate constant of around 91 x 10^{-12} cm^3/molecule/sec. Rate constants of this order are indicative of fast degradation in the troposphere (OECD, 1992b), and the compound is not expected to persist in the atmosphere.

Assuming a typical atmospheric concentration of hydroxy radicals of 5 x 10^5 radicals/cm^3, the rate constant gives an atmospheric half-life for the compound of approximately 4.5 hours.

Sediment
The new chemical has a moderate partition coefficient (Log K_{ow} = 4.5), and an estimated Log K_{oc} of 3.2. Consequently chemical released into the sewer system is likely to become bound to soils and sediments. However the binding may not be strong and the high water solubility indicates that the compound may be mobile. Also, the chemical is appreciably volatile, and in an agitated environment (e.g. in a sewage treatment plant) much is expected to be transferred to the atmosphere (see below).

Soil
Residual chemical disposed of to landfill with 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.

In respect of this point, the notifier supplied a copy of a report on the elimination of the chemical in activated sludge. The chemical was added to an aerated laboratory scale activated sludge unit (hydraulic residence time of 6 hours) at a concentration of 20 mg/L. It was concluded that >99% of the chemical was removed in the air stream, while <1% remained in the water or adsorbed to the sludge.

However, the relatively large estimate for Log K_{oc} indicates some association with the organic component of soil particles is possible. In this situation the chemical is expected to eventually be destroyed by abiotic and slow biological processes. Incineration of material containing the new chemical would produce water vapour and oxides of carbon.

Bioaccumulation
The ASTER calculations mentioned above estimate the bioaccumulation factor of 183 for the compound in fish (Fathead minnow), indicating the compound has little potential for bioaccumulation. While moderately soluble, the compound is also volatile and is therefore not expected to have prolonged residence times in the aquatic compartment.

9. EVALUATION OF TOXICOLOGICAL DATA

All animal tests were conducted according to OECD test guidelines. Testing facilities complied with the OECD principles of Good Laboratory Practice and full study reports were provided. All tests were performed on the notified chemical.

9.1 Acute Toxicity

Summary of the acute toxicity of Claritone

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} > 2 000 mg/kg	Driscoll, 1994a
acute dermal toxicity	rat	LD_{50} > 2 000 mg/kg	Driscoll, 1994b
skin irritation	rabbit	Moderate irritant at 100% concentration	Aarup, 1995
eye irritation	rabbit	Non-irritant	Braun, 1996
skin sensitisation	guinea pig	Non-sensitising	Jacobsen, 1994

9.1.1 Oral Toxicity (Driscoll, 1994a)

Species/strain:	rat/ Sprague-Dawley CD
Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	oral gavage; 2 000 mg/kg
Test method:	OECD TG 401 – limit test
Mortality:	no deaths recorded over the observation period
Clinical observations:	only females had systemic signs of toxicity including lethargy and/or hunched posture with incidents of ataxia, decreased respiratory rate, red/brown staining around the mouth, occasional body tremors and splayed gait; all animals recovered one to two days after dosing
Morphological findings:	no abnormalities noted at necropsy
LD_{50}:	> 2 000 mg/kg
Result:	the notified chemical was of very low acute oral toxicity in rats

9.1.2 Dermal Toxicity (Driscoll, 1994b)

Species/strain:	rat/ Sprague-Dawley CD
Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	semi-occlusive dressing; test material was removed after 24 hour contact; 2 000 mg/kg
Test method:	OECD TG 402 – limit test
Mortality:	no deaths were recorded over the observation period
Clinical observations:	no signs of systemic toxicity or skin irritation were noted during the observation period; no adverse effects noted on rate of bodyweight gain
Morphological findings:	no abnormalities noted at necropsy
LD_{50}:	> 2 000 mg/kg
Result:	the notified chemical was of low dermal toxicity in rats

9.1.3 Inhalation Toxicity

An acute inhalation toxicity study was not provided.

9.1.4 Skin Irritation (Aarup, 1995)

Species/strain:	rabbit/albino
Number/sex of animals:	4 females
Observation period:	35 days
Method of administration:	the study investigated 5 different test concentrations (100, 20, 10, 5 and 1% (w/w), diluted in vehicle (96% ethanol and diethyl phthalate (1:1, w/w)) in each animal; the prepared area on the back of animals was divided at random into six test sites; each animal had a semi-occlusive dressing with 0.5 mL of the appropriate concentration applied to the respective site for 4 hours, after which the test material was removed with soap and lukewarm water; skin was examined at 1, 24, 48 and 72 hours as well as 7, 14, 21, 28 and 35 days after termination of exposure
Test method:	OECD TG 404

Draize scores:

Results for the 100% test concentration:

Time after treatment (days)	***Animal #***			
	1	***2***	***3***	***4***
Erythema				
1	[a]2	2	2	2
2	2	2	2	2
3	2	2	2	2
Oedema				
1	0	1	1	0
2	1	0	1	0
3	2	1	2	2

[a] see Attachment 1 for Draize scales Draize (1959)

Comment: mean scores for the four rabbits were :

treatment	erythema	oedema
100%	2.0	0.9
20%	0.0	0.0
10%	0.1	0.0
5%	0.0	0.0
1%	0.0	0.0
vehicle	0.0	0.0

Slight to well defined skin erythema and slight oedema was observed 0-72 hours after termination of exposure at a 100% test concentration. In the period of 7-35 days after termination of exposure these rabbits had dense scales covering the test fields which gradually loosened showing intact skin underneath. One rabbit had a slight erythema 72 hours after termination of exposure at a 10% test concentration. No other abnormalities were observed.

Result: the notified chemical was moderately irritating to the skin of rabbits when applied at a 100% concentration

concentrations of 20%, 10%, 5% and 1% were not classified as skin irritants

9.1.5 Eye Irritation (Braun, 1996)

Species/strain:	rabbit/New Zealand White
Number/sex of animals:	1 male; 2 females
Observation period:	3 days
Method of administration:	0.1 mL of 100% test material (pH 5-6) was instilled into the conjunctival sac of the left eye of each animal; the right eye served as the control treated eyes were not rinsed after application
Test method:	OECD TG 405
Comment:	1 hour after application all three animals had a slight watery discharge and the sclera of the male and one of the females was hyperaemic; symptoms resolved by 24 hours no staining of the cornea, conjunctivae and sclera of the treated eyes by the test material was observed individual mean scores for corneal opacity, irideal lesions and conjunctival redness and chemosis in all animals were 0.0
Result:	the notified chemical was non-irritating to the eyes of rabbits

9.1.6.1 Skin Sensitisation (Jacobsen, 1994)

Species/strain:	guinea pig/Dunkin Hartley
Number of animals:	30 males
Induction procedure:	<u>intradermal injection</u> three pairs of 0.1 mL intradermal injections were given simultaneously into a 4 x 6 cm area of shaved dorsal skin in the scapular region; injections were: 1st pair: Freund's Complete Adjuvant (FCA):distilled water (1:1) 2nd pair: group 1: oleum arachadis group 2: 5% (w/w) test material in oleum arachadis 3rd pair: group 1: oleum arachadis:FCA (1:1) group 2: 10% (w/w) test material in oleum arachadis:FCA (1:1) <u>topical application</u> 6 days after injections, 0.5 g sodium lauryl sulphate (10% in petrolatum) was massaged into the skin; 24 hours later 0.4 mL ethanol 96% diethylphthlate (DEP) 1:1 (vehicle, group

	1), or undiluted test article (group 2), was applied as an occlusive dressing for 48 hours
Challenge procedure:	<u>challenge application</u> three weeks after intradermal induction, 0.1 mL of undiluted test material or vehicle was applied by occlusive dressing for 24 hours
Comments	challenge sites were examined 24 and 48 hours after patch removal slight and discrete erythema was observed in two animals in control group 1, 24 hours after challenge with the test material; similar signs were seen in two animals of control group 2, persisting for another 24 hours in one animal no other signs of ill health were seen
Test method:	OECD TG 406; ; Maximisation test of Magnusson and Kligman
Result:	the notified chemical was non-sensitising to the skin of guinea pigs

9.1.6.2 Cutaneous and Repetitive Cutaneous tests in humans of varying concentrations of notified chemical in 1:1 ethanol/DEP (Schrader, 1997)

General:	the notified chemical was tested for its irritant effects or ability to cause contact allergy in 37 female and 13 male human volunteers two cutaneous tests were performed at concentrations of 1% and 5% 1:1 ethanol/DEP and one repetitive cutaneous (Patch Test) was performed at a concentration of 10% 1:1 ethanol:DEP
Method of administration:	<u>1% and 5% concentration:</u> The test material was applied to the back under occlusive cutaneous dressing for 48 hours. Further assessments followed after 72 and 96 hours. The positive control was 0.3% aqueous solution of sodium dodecylsulphate. <u>10% concentration:</u> Approximately 100 mg of test material was applied to the back under occlusive dressing. After 48 hours (72 hours for weekends) the plasters were removed, residues cleaned and assessed six hours later. The test material was reapplied under the same conditions for another 48 hours and the process was repeated for a total of three weeks. This was followed by a 14 day break, after which the challenge phase

commenced by applying the test material under occlusive conditions to the contralateral skin area on the back of the volunteers. After 48 hours, dressings were removed and observations recorded on days 2, 3 and 4.
The positive control was 0.05% aqueous solution of sodium dodecylsulphate.

Comments:

1% concentration:
no erythema observed

5% concentration:
one case of slight erythema was observed

10% concentration:
no erythema observed at the end of the observation period

Results: the notified chemical was considered to be non irritating or sensitising to human skin when applied under the conditions and concentrations as described in the study

9.2 Repeated Dose Toxicity (Allard, 1996)

Species/strain: rat/Sprague Dawley

Number/sex of animals: 5/sex/ dose group; 4 groups

Method of administration: oral (gavage)

Dose/Study duration: 0, 50, 200 and 1 000 mg/kg/day for 28 consecutive days

vehicle: polyethylene glycol

Test method: OECD TG 407

Clinical observations:
No clinical signs were noted in any of the dose groups. The test material had no adverse effects on food consumption or body weight gain.

Clinical chemistry/Haematology
There were no treatment-related effects on haematology, clinical biochemistry and urinalysis data at termination of the treatment which could be considered to be of toxicological significance. However, there were a few minor findings of statistical significance but these were attributed to metabolic adaptation and deemed to have no biological relevance.

Organ weights
Both sexes in the 1 000 mg/kg/day group had significantly higher liver weights and males also had higher kidney weights.

Macroscopically, discoloured and/or enlarged livers were noted in four males and one female of the 1000 mg/kg/day group, and five females also had enlarged kidneys. The cecal dilation noted in all rats was considered to be due to the vehicle, polyethylene glycol.

Histopathology:
Minimal to slight centrilobular hepatocellular hypertrophy, regarded as an adaptive response, was found to correlate with the enlarged livers seen in all animals of the 1 000 mg/kg/day group.

Findings regarded to be treatment-related were noted in kidneys of male rats of the 200 and 1 000 mg/kg/day groups. Chiefly, these were an increase in the severity of hyaline droplet formation in the cortical tubules, accompanied by minimal to moderate granular cast formation. Slight to moderate medullary tubule dilation was also observed in all 1 000 mg/kg/day males as well as an increase in incidence and severity of tubular basophilia. These findings are typical for alpha2μ-globulin nephropathy of male rats. There were no signs of nephrotoxicity in females.

Other findings varied little in severity and incidence between control and treated groups.

Comment:
Oral administration of the notified chemical to rats resulted in no effects on mortality, clinical signs, food consumption, body weight and ophthalmological findings.

Result:
Based on renal lesions in male rats, the notified chemical was considered to have a "no-observed-adverse-effect-level" (NOAEL) of 50 mg/kg/day.

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* Reverse Mutation Assay (King, 1994)

Strains:	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 and TA1538
Concentration range:	with S9: 0 50, 150, 500, 1 500 and 5 000 μg/plate; without S9: 0 5, 15, 50, 150 and 500 μg/plate
Metabolic activation:	10% rat liver S9 fraction (Aroclor 1254-induced) in standard cofactors
Positive controls:	with S9: 2-aminoanthracene: 3 μg/plate for TA1535 and TA1537; 1 μg/plate TA1538, TA98 and TA100 without S9: sodium azide: 0.5 μg/plate for TA1535 and TA100 2-nitrofluorene: 2.5 μg/plate for TA1538 and TA98 9-aminoacridine: 50 μg/plate for TA1537
Test method:	OECD TG 471

Comment:	all doses were tested in triplicate and the experiment was repeated after 3 days evidence of toxicity was seen at the highest concentrations both in the presence and absence of S9 no significant increases in the frequency of revertants were recorded for any of the strains, at any dose level either with or without S9; all positive controls responded appropriately
Result:	the notified chemical was considered to be non-mutagenic under the conditions of the assay

9.3.2 Chromosomal aberration assay in Chinese hamster V79 cells (Czich, 1996)

Cells:	V79 Chinese hamster cells
Metabolic activation	rat liver S9 fraction (Aroclor 1254-induced) in standard cofactors, adjusted to a protein concentration of 29.8 mg/mL
Dose range:	<u>experiment 1:</u> 5-100 μg/mL, without S9 10-500 μg/mL, with S9 <u>experiment 2:</u> 2.5-75 μg/mL, without S9 10-500 μg/mL, with S9 the test material was dissolved in dimethyl sulphoxide (DMSO)
Positive controls:	cyclophosphamide 0.71 μg/mL, without S9 ethylmethane sulfonate 600 μg/mL, with S9
Test method:	OECD TG 473
Experimental design	in both experiments, cells with S9 were treated for 4 hours and cells without S9 were treated for 18 and 28 hours; cells were harvested 18 and 28 hours subsequently
Comment:	mitotic indices were reduced after treatment in both experiments, with and without S9, at the highest evaluated concentrations the test material did not increase the frequency of aberrations in both experiments, with or without S9; positive control mutagens responded appropriately
Result:	the notified chemical was considered to be non-clastogenic to V79 cells *in vitro*

9.4 Overall Assessment of Toxicological Data

The notified chemical, Claritone, has very low acute oral toxicity (LD_{50} >2 000 mg/kg) and low dermal toxicity (LD_{50} >2 000 mg/kg) in rats. When tested in rabbits, it was moderately irritating at a concentration of 100% but non-irritant at concentrations up to and including 20%. Claritone was non-irritant to the rabbit eye.

A 4 week repeated dose toxicity study established a NOAEL of 50 mg/kg/day. The prime treatment-related changes noted at 200 and 1000 mg/kg/day included centrilobular hepatocyte hypertrophy and kidney changes associated with accumulation of alpha2-microglobulin in male rats only. The latter pathological findings are not considered to represent a significant hazard to human health.

Claritone was patch tested in human volunteers. Cutaneous tests were performed at concentrations of 1% and 5% and a repetitive cutaneous test employed a concentration of 10% of the notified chemical. Study results indicated that Claritone was non-irritant and non-sensitising to human skin.

There was no genotoxic activity associated with the notified chemical when tested in the *Salmonella typhimurium* reversion assay or chromosomal aberration assay in Chinese hamster V79 cells *in vitro*.

Hazard Classification
Based on available data, Claritone meets the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999) criteria to be classified as an Irritant (Xi), and requires the risk phrase R38, "Irritating to skin". In addition, the safety phrases S24 "Avoid contact with skin" and S37 "Wear suitable gloves" should also apply.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

The notifier provided the following ecotoxicity data in support of the application. The ecotoxicity tests were performed in accordance with OECD Test Guidelines.

The tests on zebra fish were performed using solutions of the test material made up in carbon filtered tap water at measured concentrations of 0 (control), 1.2, 2.9, 7.7, 17.1 and 42.6 mg/L. The measured concentrations of the test substance analysed by GC were between 67 and 106% of the nominal concentrations, with the differences attributed to the volatility of the chemical. The tests were conducted in a semi-static (renewal) system over a 96 hour period at a controlled temperature of 22.5± 0.5ºC, with water removed daily and replaced with fresh water containing the respective concentrations of the test material. Solution analysis was conducted by gas chromatography for determination of the test chemical concentrations, and the measured concentrations were between 67 and 106% of the nominal solution concentrations. The considerable differences between the nominal and measured concentrations were attributed to the high volatility of the compound.

Test	*Species*	*Results (Measured) mg/L*
Acute Toxicity	*Brachydanio rerio*	LC_{50} (96 h) = 8.6
[OECD 203]	(Zebra fish)	NOEC (96 h) = 2.9
Acute Immobilisation	*Daphnia magna*	EC_{50} (48 h) =2.1
[OECD 202]		NOEC (48 h) = 0.7
Algal Growth Inhibition	*Scenedesmus subspicatus*	EC_{b50} (72 h) = 7.2
[OECD 201]		NOEC (72 h) = 1.7
		EC_{r50} (72 h) = 13.3
Inhibition of Bacterial	Activated Sludge	No significant inhibition – see notes
Respiration	Bacteria.	below.
[OECD 301 F]		

Seven fish were tested at each concentration, and during these tests the pH of the test solutions remained between 7.7 and 8.1, while dissolved oxygen levels remained between 6.2 and 9.6 mg/L and water hardness was around 250 mg/L as $CaCO_3$.

No erratic behaviour or fish mortality occurred over the duration of the test for measured concentrations of the test substance less than or equal to 2.9 mg/L. However, after 72 hours exposure to the 7.7 mg/L, 2 fish had died, and after 24 hours exposure to 17.1 mg/L, all fish had died. Severe behavioural aberrations, specifically apathy and fish remaining at either the bottom or the top of the tank were observed for all exposures longer than 24 hours at concentrations of 7.7 mg/L and greater. Test data was analysed using the moving average interpolation (Finney, 1978) and indicate that Claritone is moderately toxic to the zebra fish with a 96 hour LC_{50} = 8.6 mg/L. The corresponding No Observed Effect Concentration (NOEC) was 2.9 mg/L.

The acute immobilisation tests on daphnia were performed using solutions of the test material in a static non renewal system over a 48 hour period at a controlled temperature of 20.3 ± 0.1ºC. Five solutions of the chemical with (geometric mean) measured concentrations of 0.7, 1.2, 2.4, 6.0 and 15.0 mg/L were tested, with one control. Test substance concentrations measured by GC were between 53% and 75% of the nominal concentrations, and this was attributed to the volatility of the chemical. Five juvenile daphnia were tested at each concentration, with four replicate tests conducted at each concentration. During these tests the pH of the test solutions remained between 7.7 and 8.0, while dissolved oxygen levels were between 7.4 and 8.9 mg/L and hardness was around 250 mg/L as $CaCO_3$.

No reduction in daphnia mobility was observed after 24 hours for the test concentration of 2.5 mg/L, but at higher test concentrations and exposure times, significant immobility was observed. After 48 hours exposure to 2.5 mg/L, 3 daphnia were immobile, while all animals were immobilised after 48 hours exposure to 6.0 mg/L. Test results were analysed using probit analysis (Finney, 1971) and indicate that Claritone is moderately toxic to daphnia with a 48 hour EC50 of 2.1 mg/L and a corresponding 48 hour NOEC of 0.7 mg/L.

No test report on daphnia reproduction was submitted. However, the acute toxicity curve is not very steep (i.e. compare the 48 hour NOEC of 0.7 mg/L with the concentration of 6.0

mg/L for which 100% immobilisation was observed), suggesting that chronic effects at low concentrations could be anticipated. Similarly the QSAR estimates (see further below) for acute and chronic toxic effects against Fathead minnow indicate chronic effects are to be expected at concentrations 5-6 times lower than the LC_{50} for this species. Consequently, is likely that a similar pattern of acute versus chronic toxicity could be expected for daphnia and that chronic effects could be expected at about 0.5 mg/L.

A test on the inhibition of algal growth was also conducted on *Scenedesmus subspicatus* over a 72 hour incubation period at 22.5 ± 0.2ºC using nominal concentrations for the test material of 0 (control), 1.4, 3.0, 6.4, 13.8 and 30.0 mg/L in distilled water. The concentration of the test substance in the media was determined at 0, 24, 48 and 72 hours after commencement of the test. The (arithmetic) mean measured concentrations were between 27 and 46% of the nominal concentrations, with the difference attributed to compound volatility. The results were analysed using Dunnet's test (Finney, 1978) and show the new chemical is at least moderately toxic to this species of green algae, with the 72 hour (biomass) Ec_b50 = 7.2 mg/L and a NOEC = 1.7 mg/L.

No dedicated test for the inhibition of bacterial respiration was conducted but a subsidiary test was performed as part of the tests for ready biodegradability (OECD 301F). Results indicated no significant inhibition of respiration when the new chemical was present at 3010 mg/L of the Theoretical Oxygen Demand (i.e. around 100 mg/L of the new chemical).

The QASR calculations of the ASTER database (USEPA, 1998) gave predicted acute toxicity LC_{50} data for several fish species including Rainbow trout (3.2 mg/L), Fathead minnow (8.0 mg/L), Bluegill (6.5 mg/L), and Channel catfish (3.5 mg/L). The calculations gave an acute EC_{50} of 4.7 mg/L for immobilisation of daphnia and a chronic 32 day Maximum Acceptable Toxic Concentration (MATC) of 1.3 mg/L for Fathead minnow. These results are in reasonable accord with the experimental data and support the conclusion that the new chemical is at least moderately toxic to aquatic species. The ratio of the estimated values for LC_{50} (96 h) and 32 day MATC indicate chronic toxic effects to aquatic species could be anticipated at concentrations less than one order of magnitude below the 50% lethal concentrations.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

All new chemical will be used as an ingredient of domestic cleaning and personal care formulations, and much of the material would eventually be released into domestic sewage systems as consequence of product use. However, as the chemical is volatile, a high proportion is likely to enter the atmosphere.

The ecotoxicity data indicates that the new chemical is toxic to those aquatic species against which it was tested. Based on maximum annual imports of 200 kg, all of which is eventually released to sewer, the daily release on a nationwide basis is 2.8 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 1.0 µg/L. When released to receiving waters the concentration is generally understood to be further reduced by a factor of at least 10, so the Predicted Environmental Concentration (PEC) after final release is around 0.1 µg/L. This PEC is four orders of magnitude less than

the concentrations at which the compound is likely to demonstrate acute toxicity to aquatic species, and the safety margin for expected chronic toxicity levels is also large at around 5,000.

The SimpleTreat and Level 1 Mackay calculations mentioned above indicate much of the chemical would eventually partition into the atmosphere and be destroyed by reactions with hydroxyl free radicals. This is expected to be the dominant mechanism for removal of the compound from the environment and the final degradation products are expected to be to water and oxides of carbon. The biological and abiotic mechanisms (particularly photodegradation reactions) would operate to continuously remove the chemical from the environmental compartments and overall environmental concentrations would be unlikely to increase with prolonged release of the chemical.

The appreciable values for Log K_{ow} (4.5) and Log K_{oc} (estimated as 3.7) indicate moderate affinity for the organic component of soils and sediments. However, the moderate water solubility and medium value for Log K_{oc} indicate that if assimilated into soils and sediments, the notified chemical is likely to be mobile. Nevertheless chemical associated with soils and sediments is expected to be degraded through slow biological and abiotic processes.

Although the notified chemical is moderately soluble in water (59.1 mg/L) persistence in the water compartment is expected to be low through volatilisation to the atmosphere and degradation through photochemical processes. The compound is not anticipated to bioaccumulate.

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

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The notified chemical is determined to be a hazardous substance, according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999) and the risk phrase R38, "Irritating to skin" should be assigned.

The acute oral toxicity of Claritone is very low (LD_{50} > 2000 mg/kg) and the acute dermal toxicity is low (LD_{50} > 2000 mg/kg). It is neither an eye irritant in rabbits nor a skin sensitiser in guinea pigs. No evidence of genotoxicity was observed in two *in vitro* genotoxicity tests. The major hazard from acute exposure arises from the skin irritant effects. Claritone was a moderate skin irritant at 100% and non-irritant at concentrations up to and including 20%.

For longer-term systemic effects, in a 28 day feeding study in rats, the major treatment related changes included hypertrophy of the liver and renal changes in male rats (only). The latter pathological findings are not considered relevant to humans. The NOAEL was determined at 50 mg/kg/day.

Occupational Health and Safety
Worker exposure during transport and storage will only occur in the event of an accident, where the packaging is breached.

When mixing the notified chemical to produce fragrance compounds, dermal and ocular exposure is possible through splashing, particularly if it is an open process. During mixing, the chemical decanted from the drum is at 100% and a hazardous substance. Workers will need to wear personal protective clothing and chemical resistant gloves to prevent contamination with the chemical. Once mixed with other fragrance compound ingredients, the maximum concentration of the notified chemical present in the mixture is 10%. At this concentration, the chemical in solution is not expected to be a skin irritant. Significant inhalation exposure to the notified chemical is not expected due to its low vapour pressure and physical state (liquid). Exhaust ventilation is expected to be in place, to minimise worker exposure to any vapours. Workers are likely to carry out this work on a regular basis (about 50 times per year on average) however the duration of handling is short (up to 2.5 hours per batch). Details on the packaging process for fragrance compounds were not provided, however, it is more likely to be an automated than a manual activity, therefore, significant worker exposure is not likely.

The incorporation of fragrance compounds containing the notified chemical into consumer goods is typically carried out within a closed plant at several sites around Australia. The notifier did not provide details on the incorporation process. The chemical within the fragrance compound will be at a maximum of 10% and not a hazardous substance on this basis. The final concentration of the notified chemical in the consumer products is low ranging from 0.00001% to 2% (average 0.01%) and exposure to this level is not expected to result in adverse health effects in workers.

Public health
Minimal public exposure is expected from transport, storage, production of fragrance compounds and consumer products and disposal.

Members of the public will make dermal and inhalation contact and possibly eye contact with the notified chemical contained through handling the end use products. However, exposure is likely to be negligible because of the low concentration of the notified chemical in consumer products (<2%, with the average concentration 0.01%). At the concentrations found in consumer products, the notified chemical would not be a skin or eye irritant.

Overall, Claritone is not expected to pose a significant hazard to public health when used in the manner proposed in the notification statement.

13. RECOMMENDATIONS

To minimise occupational exposure to Claritone, the following guidelines and precautions should be observed:

- Safety goggles should be selected and fitted in accordance with Australian Standard (AS) 1336 (Standards Australia, 1994) to comply with Australian/New Zealand Standard (AS/NZS) 1337 (Standards Australia/Standards New Zealand, 1992); industrial clothing should conform to the specifications detailed in AS 2919 (Standards Australia, 1987) and AS 3765.2 (Standards Australia, 1990); impermeable gloves should conform to AS/NZS 2161.2 (Standards Australia/Standards New Zealand, 1998); all occupational footwear should conform to AS/NZS 2210 (Standards Australia/Standards New Zealand, 1994);

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

- Good personal hygiene should be practised to minimise the potential for ingestion;

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

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.

If the conditions of use are varied, then greater exposure of the public may occur. In such circumstances, further information may be required to assess the hazards to public health.

14. MATERIAL SAFETY DATA SHEET

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

This MSDS was provided by the applicant as part of the notification statement. It is reproduced here as a matter of public record. The accuracy of this information remains the responsibility of the applicant.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

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

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Attachment 1

The Draize Scale for evaluation of skin reactions is as follows:

Erythema Formation	*Rating*	*Oedema Formation*	*Rating*
No erythema	0	No oedema	0
Very slight erythema (barely perceptible)	1	Very slight oedema (barely perceptible)	1
Well-defined erythema	2	Slight oedema (edges of area well-defined by definite raising	2
Moderate to severe erythema	3	Moderate oedema (raised approx. 1 mm)	3
Severe erythema (beet redness)	4	Severe oedema (raised more than 1 mm and extending beyond area of exposure)	4

The Draize scale for evaluation of eye reactions is as follows:

CORNEA

Opacity	*Rating*	*Area of Cornea involved*	*Rating*
No opacity	0 none	25% or less (not zero)	1
Diffuse area, details of iris clearly visible	1 slight	25% to 50%	2
Easily visible translucent areas, details of iris slightly obscure	2 mild	50% to 75%	3
Opalescent areas, no details of iris visible, size of pupil barely discernible	3 moderate	Greater than 75%	4
Opaque, iris invisible	4 severe		

CONJUNCTIVAE

Redness	*Rating*	*Chemosis*	*Rating*	*Discharge*	*Rating*
Vessels normal	0 none	No swelling	0 none	No discharge	0 none
Vessels definitely injected above normal	1 slight	Any swelling above normal	1 slight	Any amount different from normal	1 slight
More diffuse, deeper crimson red with individual vessels not easily discernible	2 mod.	Obvious swelling with partial eversion of lids	2 mild	Discharge with moistening of lids and adjacent hairs	2 mod.
		Swelling with lids half-closed	3 mod.	Discharge with moistening of lids and hairs and considerable area around eye	3 severe
Diffuse beefy red	3 severe	Swelling with lids half-closed to completely closed	4 severe		

IRIS

Values	*Rating*
Normal	0 none
Folds above normal, congestion, swelling, circumcorneal injection, iris reacts to light	1 slight
No reaction to light, haemorrhage, gross destruction	2 severe