

File No: NA/640

2 February 2000

**NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION  
AND ASSESSMENT SCHEME**

**FULL PUBLIC REPORT**

**Camonal**

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Director  
Chemicals Notification and Assessment

**FULL PUBLIC REPORT****Camonal****1. APPLICANT**

Quest International Australia Pty Limited of 6 Britton Street SMITHFIELD NSW 2164 has submitted a limited notification statement in support of their application for an assessment certificate for Camonal.

**2. IDENTITY OF THE CHEMICAL**

**Chemical Name:** 2-isobutyl-5-methyl 1,3-dioxane

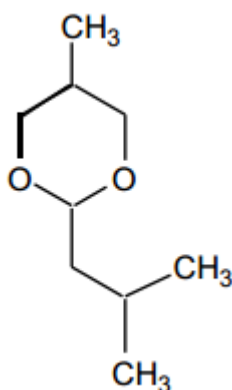
**Chemical Abstracts Service  
(CAS) Registry No.:** 166301-22-0

**Other Names:** 2-(2-methylpropyl)-5-methyl 1,3-dioxane

**Trade Name:** Camonal

**Molecular Formula:** C<sub>9</sub>H<sub>18</sub>O<sub>2</sub>

**Structural Formula:**



<b>Molecular Weight:</b>	158
<b>Method of Detection and Determination:</b>	NMR, UV, IR, MS and GC

***Comments on Identity***

Camonal is a mixture of cis and trans isomers present in a ratio of approximately 80:20, respectively. The commercial product also contains a trace of the impurity 2-isobutyl-4-methyl 1,3-dioxane (CAS No. 166301-21-9) which results from traces of butan-1,3-diol in the precursor compounds.

### **3. PHYSICAL AND CHEMICAL PROPERTIES**

<b>Appearance at 20°C and 101.3 kPa:</b>	clear colourless liquid
<b>Freezing Point:</b>	< -20°C
<b>Relative Density:</b>	0.91 at 19°C
<b>Vapour Pressure:</b>	approximately 0.13 kPa at 25°C
<b>Water Solubility:</b>	2 710 mg/L at 20°C
<b>Henry's Law Constant:</b>	7.4 Pa m <sup>3</sup> /mole
<b>Partition Co-efficient (n-octanol/water):</b>	log P <sub>ow</sub> = 3.07 at 20°C
<b>Hydrolysis as a Function of pH:</b>	not determined
<b>Adsorption/Desorption:</b>	not determined
<b>Dissociation Constant:</b>	not determined
<b>Flash Point:</b>	approximately 59°C
<b>Flammability Limits:</b>	not determined, however, can sustain a fire
<b>Autoignition Temperature:</b>	approximately 240°C
<b>Explosive Properties:</b>	not determined
<b>Reactivity/Stability:</b>	not determined

### ***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, equilibrating for at least 24 hours at 20°C, then separating the aqueous and non aqueous layers by centrifugation. The content of the new chemical in the aqueous phase was determined by gas chromatography. The average of three separate determinations gave the water solubility as  $2\,710 \pm 120$  mg/L at 20°C.

The Henry's law constant (H) of  $5.566 \text{ Pa}\cdot\text{m}^3/\text{mol}$  was calculated from the molecular weight (MW), the measured water solubility and vapour pressure through the equation:

$$H = \text{MW (g/mole)} \times \text{Vapour Pressure (Pa)} / \text{Water solubility (g/L)}.$$

The compound contains two cyclic ether linkages which are susceptible to slow hydrolysis under acidic conditions. The rate of hydrolytic degradation of aqueous solutions containing measured concentrations of the test material (1 880-2 120 mg/L) were determined in duplicate at pH 4, 7 and 9 at 25°C over a five day test period. Samples were analysed for the undegraded Calomal at three different times after commencement of the tests (approximately 24 h, 48 h and 120 h) using gas chromatography, and the percentage loss was used to derive the half lives listed above assuming pseudo first order kinetics. This data is interpreted to indicate a half life of between 36 days and greater than one year at 25°C under the usual environmental pH conditions.

The n-octanol/water partition coefficient was determined using the HPLC method, where the retention time of the test compound on C<sub>18</sub> columns is compared with those of eight reference compounds with known values for Log P<sub>OW</sub> ranging from 1.1 (benzyl alcohol) to 6.2 (DDT). The determined value of Log P<sub>OW</sub> = 3.07 indicates the new chemical has some affinity for hydrocarbon like environments.

The notifier indicated that Log K<sub>OC</sub> was not determined due to the volatility of the compound. However, the value of Log K<sub>OC</sub> can be estimated using the relationship:

$$\text{Log K}_{\text{OC}} = 0.81 \times \text{Log P}_{\text{OW}} + 0.1$$

which provides an estimate of 2.59 for this quantity. This relationship is appropriate for compounds containing predominantly hydrophobic functionalities. It is one of the quantitative structure activity relationships (QSAR) recommended by the EEC for calculating K<sub>OC</sub> of organic compounds (European Commission, 1996b). The calculated value for Log K<sub>OC</sub> as 2.59 indicates that the chemical has a slight tendency to partition into the organic component of soils and sediments, and become associated with these materials.

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

The surface tension of an aqueous solution containing approximately 990 mg/L (37% saturation) of the test substance was 59.5 mN/m at  $19 \pm 0.5^\circ\text{C}$  (water=72.6 mN/m), which indicates the material is moderately surface active.

Calculations based on the molecular structure using the QSARs of the US Environment Protection Agency ASTER database (US Environment Protection Agency, 1998) furnished the following estimates for environmentally relevant physico-chemical parameters. Where comparison with data supplied by the notifier is possible, the agreement is good except for the estimated value of Log P<sub>ow</sub>.

**ASTER DATA (all calculated using QSARs)**

<b>PROPERTY</b>	<b>QSAR ESTIMATE</b>
Boiling Point:	180°C
Vapour Pressure:	0.941 mm of Hg (125 Pa)
Water Solubility:	2 730 mg/L
Henry's Law Constant:	7.27 Pa.m <sup>3</sup> /mole
Log P <sub>ow</sub> :	2.08
Log K <sub>oc</sub> :	2.47
Hydrolysis:	Hydrolytic degradation unlikely.

#### **4. PURITY OF THE CHEMICAL**

<b>Degree of Purity:</b>	> 99.8% (combined cis and trans isomers)
<b>Toxic or Hazardous Impurities:</b>	none
<b>Non-hazardous Impurities (&gt; 1% by weight):</b>	none
<b>Additives/Adjuvants:</b>	none
<b>Degradation Products:</b>	thermal degradation to water and oxides of carbon.

## 5. USE, VOLUME AND FORMULATION

The notified chemical functions as a fragrance enhancer in domestic, toilet, and cosmetic products, and will be used in the manufacture of a variety of personal and household consumer products, such as soaps, detergents and air fresheners. The notified chemical will comprise 0.1 % to 25 % of the compounded fragrances, with a typical level being around 5 %. The end use products will reportedly commonly contain 1-2 % of the fragrance mixture, therefore a maximum of 0.5 % of the notified chemical. This maximum concentration is only likely to be approached in solid air fresheners.

The compounded fragrances will not be manufactured in Australia. The import volumes are estimated to be 250 kg per annum in the first 3 years, possibly reaching 500 kg per annum after this time.

## 6. OCCUPATIONAL EXPOSURE

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

### *Formulation*

The fragrances will be blended into the consumer products by a number of formulators using a variety of mixing techniques. It is estimated that between 5 and 20 process workers will be exposed to the notified chemical at each formulation plant.

The notifier has provided a description of the type of operation which will be carried out in the production of several types of product containing the notified chemical. The examples given are for production of air fresheners, soap bars and liquid soaps. The fragrance mixture used in soap manufacture is expected to include a maximum of 2 % notified chemical; while the fragrance mixture used in air fresheners will contain up to 25 % notified chemical.

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

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

### *End-use*

The notifier did not provide details of end-use. Industrial cleaners will use the end-use products such as spray, liquid and soap form gel on an 8 hours per day basis. Exposure to the products containing the fragrances during end use is expected to be low as the maximum

concentration of the notified chemical in the end-use products is 0.5%, and this in air fresheners. The main route of exposure in the end users is considered to be dermal although the end-use products included air fresheners where limited inhalation exposure is expected.

## **7. PUBLIC EXPOSURE**

No information has been submitted on importation containers. It is expected that during transport and storage, exposure of the general public to the notified chemical in the compounded fragrances will not occur, except in the event of accidental spills. Documentation on the handling of accidental spills was not submitted.

As the notified chemical will be used in a wide range of household products (soaps, detergents, and air fresheners containing compounded fragrances), there will be widespread public exposure. Routes of exposure will include inhalation (of air fresheners), ocular, and systemic absorption across the skin (molecular wt 158), which is likely to be the main route of exposure.

The notifier has supplied a risk assessment where typical exposures from cosmetic products, soaps/shower gels, and household products have been calculated, based on European usage figures. Assuming a notified chemical concentration of 0.03% in household products, and 0.006% in cosmetic products and soap/shower gels, 10% absorption through the skin, and a 60 kg body weight, a person applying 10g of a cosmetic cream, once daily, would receive a systemic exposure of 0.001 mg/kg/day. A person using 5g of soap/shower gel per day, assuming 10% remains on the skin, would receive a systemic exposure of 0.00005 mg/kg/day, and a person using 10g of a household product, 1% of which is in direct contact with the skin, would receive a systemic exposure of 0.00005 mg/kg/day. If these were the same person, the total estimated exposure would be 0.0011 mg/kg/day. Therefore, public exposure from the proposed use is expected to be low.

## **8. ENVIRONMENTAL EXPOSURE**

### **Release**

The notifier indicated that production activities involving use of the new chemical would be performed by a number of different companies (number and locations were not known by the notifier at the time of notification), and it is expected that production activities will take place in purpose constructed facilities.

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

The empty steel and polythene drums of fragrance will be washed and reused. No estimates of the amount of residual chemical left in the drums was presented in the application, but it is

estimated that this could amount to 0.05 - 0.1% of the import quantity, or around 250-500 g per annum, and it is probable that this would also be washed into the sewer.

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

However, the new chemical is a fragrance for use in domestic cleaning and personal care products, and consequently all will be eventually released into the environment as a result of normal product usage. It is expected that a high proportion of the chemical would be released into the sewerage system, although due to the high 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.

## **Fate**

### ***Biodegradation***

The notifier provided a laboratory report on the assessment of the biodegradation of Camonal conducted in accordance with the OECD Test Guideline TG 301F (Manometric Respirometry Test). The results of this test (performed in triplicate) indicated <13% loss of initial chemical oxygen demand (COD) of the test material after 28 days, and accordingly the Camonal cannot be classed as either readily biodegradable or as inherently biodegradable.

### ***Models***

All the new chemical will eventually be released into the environment, and the majority could be expected to be discharged into sewerage systems. However, once released in this manner the high vapour pressure indicates significant partitioning into the atmospheric compartment. For that proportion of the chemical which reaches sewage treatment plants (ie is not volatilised or otherwise destroyed during passage to the plant), the notifier presented the results of calculations from the SimpleTreat Model (European Commission, 1996a). These estimates were based on the chemical having a calculated Henry's constant of 7.4 Pa.m<sup>3</sup>/mole, a Log P<sub>OW</sub> of 3.1 and being not biodegradable. The results indicated that the chemical would be expected to partition into the air, water and sewer sludge compartments as follows –

<b>Air</b>	<b>Water</b>	<b>Sewer Plant Sludge</b>
5%	88%	7%

Mackay Level 1 calculations from the ASTER database (US Environment Protection Agency, 1998) indicate that at equilibrium the chemical would partition primarily to the atmosphere. The Mackay model assumes that an equilibrium is established between all phases. In the environment an equilibrium state will not be reached as chemical which reaches the atmosphere will be effectively removed from the system by diffusion and degradation - see further below.

The partitioning into the various environmental compartments resulting from this model is:



Atmospheric compartment	71.7%
Soil compartment	0.27%
Sediment compartment	0.25%
Water compartment	28.3%
Aquatic biota compartment	0.00%

Considering the assumptions and approximations inherent in both these models, the differences between the two sets of results cannot be considered surprising or contradictory, and can be primarily attributed to the order of magnitude difference between the measured value of Log P<sub>ow</sub> (ie 3.07) and that calculated by QSAR (2.08). Both methodologies indicate partitioning to the atmosphere. However, while the Mackay calculations indicate significantly more partitioning to this compartment, it should be appreciated that as the compound is destroyed in the atmosphere through reaction with hydroxyl radicals (see below), it would be replenished from that in the water and sediments, and the equilibrium distributions would be maintained.

### ***Atmosphere***

Once released to the atmosphere it is considered that the chemical would be quickly decomposed through photolytically promoted free radical reactions. Hence, over time the sediment/water and water/air partitioning will be driven toward the loss of the chemical to the atmosphere. In the atmosphere it is likely that the substance will be degraded through reaction with hydroxyl radicals (through hydrogen abstraction mechanisms). A calculation based on the OECD methods (OECD, 1992), indicates that in the troposphere the new chemical would react in this manner with a rate constant estimated as  $37 \times 10^{-12}$  cm<sup>3</sup>/molecule/sec. Rate constants of this order are indicative of fast degradation (OECD, 1992), and the compound is not expected to persist in the atmosphere.

### ***Sediment***

The new chemical is hydrophobic in character with Log P<sub>ow</sub> 3.07, and estimated Log K<sub>oc</sub> 2.59. Consequently, when released into the sewer system, some chemical may remain associated with the organic component of the particulate matter present in the raw sewage, and eventually become incorporated into sediments. Here it would be slowly degraded through biological and abiotic processes to water, carbon dioxide and methane.

### ***Soil***

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

### ***Bioaccumulation***

The ASTER calculations mentioned above also provide an estimated bioaccumulation factor of 17 for the compound in fish (fathead minnow), indicating little potential for

bioaccumulation. While reasonably soluble, the compound is also volatile and is therefore not expected to have prolonged residence times in the aquatic compartment.

## 9. EVALUATION OF TOXICOLOGICAL DATA

### 9.1 Acute Toxicity

#### Summary of the acute toxicity of Camonal.

<i>Test</i>	<i>Species</i>	<i>Outcome</i>	<i>Reference</i>
acute oral toxicity	rat	LD <sub>50</sub> > 2 000 mg/kg	(McRae, 1996b)
acute dermal toxicity	rat	LD <sub>50</sub> > 2 000 mg/kg	(McRae, 1996a)
skin irritation	rabbit	a moderate irritant	(Parcell, 1996b)
eye irritation	rabbit	a slight irritant	(Parcell, 1996a)
skin sensitisation	guinea pig	not a skin sensitiser	(Selbie & Lea, 1996)

#### 9.1.1 Oral Toxicity (McRae, 1996b)

<i>Species/strain:</i>	rat/Sprague-Dawley
<i>Number/sex of animals:</i>	5/sex
<i>Observation period:</i>	14 days
<i>Method of administration:</i>	oral (gavage)
<i>Clinical observations:</i>	piloerection and increased salivation were observed in all rats within 7 minutes of dosing, accompanied at this time in one male and all females by hunched posture; piloerection persisted in all animals and was accompanied in all males on day 2 by soft to liquid faeces; animals had recovered by day 3 and 4 for males and females, respectively.
<i>Mortality:</i>	nil
<i>Morphological findings:</i>	nil
<i>Test method:</i>	limit test, OECD TG 401 (Organisation for Economic Co-operation and Development, 1995-1996)
<i>LD<sub>50</sub>:</i>	> 2 000 mg/kg

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

### 9.1.2 Dermal Toxicity (McRae, 1996a)

*Species/strain:* rat/Sprague-Dawley

*Number/sex of animals:* 5/sex

*Observation period:* 14 days

*Method of administration:* the notified chemical was spread evenly over the clipped skin, then covered with an occlusive dressing for 24 hours.

*Clinical observations:* slightly low bodyweight gains were recorded for 1 male and 2 females on day 8, and 2 males and 1 female on day 15.

*Mortality:* nil

*Morphological findings:* nil

*Test method:* OECD TG 402 (Organisation for Economic Co-operation and Development, 1995-1996)

*LD<sub>50</sub>:* > 2 000 mg/kg

*Remarks:* the Draize scores were all zero in rats at 2 000 mg/kg for 15 days in this study

*Result:* the notified chemical was of low dermal toxicity in rats

### 9.1.3 Inhalation Toxicity

No inhalation toxicity study was available.

### 9.1.4 Skin Irritation (Parcell, 1996b)

*Species/strain:* rabbit/New Zealand White

*Number/sex of animals:* 3 males

*Observation period:* 13 days

*Method of administration:* the notified chemical (0.5 mL) was applied to intact skin under a semi-occlusive dressing for 4 hours.

*Draize scores (Draize, 1959):*

<i>Animal #</i>	<i>Time after treatment (days)</i>												
	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>
<b><i>Erythema</i></b>													
1	1	2	2	2	2	2	2	1	1	1	1	1	0
2	1	1	1	1	1	0	0	0	0	0			
3	2	2	2	2	2	2	2	2	2	1	1	1	0
<b><i>Oedema</i></b>													
1	1	1	1	1	1	1	1	0	0	0	0	0	0
2	1	1	0	0	0	0	0	0	0	0			
3	2	2	2	2	2	2	2	1	1	0	0	0	0

<sup>a</sup> see Attachment 1 for Draize scales

*Test method:*

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

*Result:*

the notified chemical was a moderate irritant to the skin of rabbits and classified as a hazardous substance based on the persistence of well defined irritant effects

#### 9.1.5 Eye Irritation (Parcell, 1996a)

*Species/strain:*

rabbit/New Zealand White

*Number/sex of animals:*

3 males

*Observation period:*

7 days

*Method of administration:*

the notified chemical (0.1 mL) was placed into the lower everted lid of one eye of each animal

*Draize scores (Draize, 1959):*

<i>Animal</i>	<i>Time after instillation</i>									
	<i>1 day</i>		<i>2 days</i>		<i>3 days</i>		<i>4 days</i>		<i>7 days</i>	
<i>Conjunctiva</i>	<i>r</i>	<i>c</i>	<i>r</i>	<i>c</i>	<i>r</i>	<i>c</i>	<i>r</i>	<i>c</i>	<i>r</i>	<i>c</i>
1	2	1	1	1	1	0	0	0	0	0
2	1	0	0	0	0	0	0	0	0	0
3	2	1	1	0	1	0	1	0	0	0

<sup>1</sup> see Attachment 1 for Draize scales  
r redness c chemosis

Draize scores for the cornea and iris were zero for all animals up to 7 days

*Test method:*

OECD TG 405 (Organisation for Economic Co-operation and Development, 1995-1996)

*Result:*

the notified chemical was a slight irritant to the eyes of rabbits

#### 9.1.6 Skin Sensitisation (Selbie & Lea, 1996)

*Species/strain:*

guinea pig/Albino Dunkin Hartley

*Number of animals:*

10/sex (test), 5/sex (control)

*Induction procedure:*

Day 1 (intradermal injection): 3 pairs of injections were made.

- a 1:1 mix of Freund's Complete Adjuvant (FCA) with 0.9% (w/v) saline;
- 1% (w/v) notified chemical in corn oil;
- 2% (w/v) notified chemical in corn oil mixed 1:1 with FCA to achieve 1% notified chemical;

Day 8 (occluded patch application):

- a filter paper saturated with the notified chemical was applied to clipped skin under adhesive tape for 48 hours.

*Challenge procedure:*

Day 21: a filter paper saturated with 10% (w/v) notified chemical in 70% acetone/30% polyethylene glycol 400 was applied under occluded patch to clipped and shaved flank for 24 hours.

*Challenge outcome:*

<i>Challenge concentration</i>	<i>Test animals</i>		<i>Control animals</i>	
	<i>24 hours*</i>	<i>48 hours*</i>	<i>24 hours</i>	<i>48 hours</i>
10%	**0/20	0/20	0/10	0/10

\* time after patch removal

\*\* number of animals exhibiting positive response

*Test method:* Magnusson and Kligman maximisation test, OECD TG 406 (Organisation for Economic Co-operation and Development, 1995-1996)

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

## 9.2 Repeated Dose Toxicity (Allan, 1996)

*Species/strain:* rat/Sprague-Dawley

*Number/sex of animals:* 5/sex for each dose group, additional 5/sex (control and 1 000 mg/kg/day) satellite groups with a 4 week recovery period

*Method of administration:* oral (gavage)

*Dose/Study duration::* animals were treated once daily for 28 consecutive days (vehicle: corn oil);  
group 1: control  
group 2: 15 mg/kg/day;  
group 3: 150 mg/kg/day;  
group 4: 1 000 mg/kg/day.

*Clinical observations:* bodyweight gains were lower than controls for group 4 males; no significant behavioural changes observed.

*Clinical chemistry/Haematology* higher alkaline phosphatase levels were recorded for group 4 males at week 4, and higher triglyceride levels for group 4 females; creatine phosphokinase levels were higher than control for group 4 males and lower than control for group 4 females.

no significant changes in biochemical parameters in recovery animals; no significant changes in haematological parameters in any animal.

*Organ weights:* increased relative liver weights were recorded for group 4 males and females, and increased relative

kidney weights in group 4 females at termination. In recovery animals, decreased absolute liver weight in males at 1 000 mg/kg/day and slight decrease in absolute spleen and kidney weights were observed but all effects were within historical control range.

*Histopathology:*

Centrilobular hepatocyte hypertrophy and slight follicular epithelial hypertrophy in the thyroid seen in group 4 males and females; effects not observed in recovery group.

an increased incidence and degree of eosinophilic inclusions in the kidneys in group 4 males, effects present to a lesser degree in 4 week recovery animals; this change was not considered by authors to be predictive of a similar effect in humans.

*Test method:*

OECD TG 407 (Organisation for Economic Co-operation and Development, 1995-1996)

*Result:*

the study authors considered the liver effects to be adaptive in nature, and the thyroid effects linked to liver changes. The kidney changes were considered indicative of light hydrocarbon nephropathy syndrome.

Based on the treatment related changes in liver, kidney and thyroid at the high dose of 1 000 mg/kg/day, the NOEL level is considered to be 150 mg/kg/day.

### **9.3 Genotoxicity**

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

*Strains:*

TA1535, TA1537, TA100 and TA98

*Concentration range:*

toxicity assay: 0.5, 5, 50, 500 and 5 000 µg/plate both in the presence and absence of metabolic activation;

mutation assay: 15, 50, 150, 500, 1 500 and 5 000 µg/plate in the presence and absence of metabolic activation.

*Test method:*

OECD 471 (Organisation for Economic Co-operation and Development, 1995-1996)

<i>Comments:</i>	<p>no increase in the number of revertant colonies occurred with any of the 4 strains of bacteria at the concentrations tested either in the presence or absence of metabolic activation; the ability of the test system to detect known mutagens was demonstrated with positive controls.</p> <p>all strains showed toxicity at 5 000 µg/plate both in the presence and absence of S-9 and slight toxicity at 500 µg/plate in the presence of S-9.</p>
<i>Result:</i>	under the study conditions, the notified chemical did not induce mutations in the bacteria strains tested.

### 9.3.2 Metaphase Chromosome Analysis of Human Lymphocytes Cultured *in vitro* (Akhurst, 1996)

<i>Species/strain:</i>	cultured human lymphocytes
<i>Concentration range:</i>	<p>first test: 156.3-625 µg/mL (without S-9, 21 hour harvest), 312.5-1 250 µg/mL (with S-9, 21 hour harvest);</p> <p>second test: 156.3-625 µg/mL (without S-9, 21 hour harvest), 625-1 500 µg/mL (with S-9, 21 hour harvest), 625 µg/mL (without S-9, 45 hour harvest), 1 500 µg/mL (with S-9, 45 hour harvest).</p>
<i>Test method:</i>	OECD TG 473 (Organisation for Economic Co-operation and Development, 1995-1996)
<i>Comments:</i>	the notified chemical caused no statistically significant increases in the proportion of metaphase figures containing chromosomal aberrations at any dose level when compared with the solvent control in both the absence and presence of S-9. All positive controls caused large statistically significant increases in the proportion of aberrant cells.
<i>Result:</i>	the notified chemical showed no evidence of clastogenic activity in this <i>in vitro</i> cytogenetic test system.



## 9.4 Overall Assessment of Toxicological Data

Camonal was of very low acute oral toxicity ( $LD_{50} > 2\,000$  mg/kg) and low acute dermal toxicity ( $LD_{50} > 2\,000$  mg/kg) in rats. It is a slight eye irritant and a moderate skin irritant in rabbits. When tested in guinea pigs, the notified chemical was not a skin sensitiser.

A 28 day oral repeat dose study showed treatment related changes in the liver, thyroid and kidney at 1 000 mg/kg/day. Based on these effects, the NOEL for Camonal was established at 150 mg/kg/day. There was evidence of complete recovery in the liver and thyroid and at least partial recovery from the kidney changes.

The notified chemical was not mutagenic in a *Salmonella typhimurium* reverse mutation assay and was not clastogenic in cultured human lymphocytes *in vitro*.

According to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999), the notified chemical is classified as a hazardous substance on the basis of persistent and well defined skin irritant effects (risk phrase R38).

## 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.

Test	Species	Results (Measured) (mg/L)
Acute Toxicity [OECD 203]	<i>Brachydanio rerio</i> (Zebra fish)	$LC_{50}$ (96 h) > 68.4 31.4 > NOEC (96 h) > 16.3
Acute Immobilisation [OECD 202]	<i>Daphnia magna</i>	$EC_{50}$ (48 h) > 52 NOEC (48 h) > 52
Algal Growth Inhibition [OECD 201]	<i>Scenedesmus subspicatus</i>	NOEC (72 h) > 42

The tests on zebra fish were performed using solutions of the test material made up in carbon filtered tap water at concentrations of 0 (control), 4.3, 8.6, 16.3, 31.4, and 68.4 mg/L. The tests were conducted in a semi-static (renewal) system over a 96 hour period at a controlled temperature of 26°C, with water removed daily and replaced with fresh water containing the respective concentrations of the test material. Solution analysis was conducted daily by gas chromatography for determination of the test chemical concentrations. Seven fish were tested at each concentration. During these tests the pH of the test solutions was always between 7.4 and 8.0, while dissolved oxygen levels were always between 6.6 and 7.2 mg/L and water hardness, measured as  $CaCO_3$ , was between 107 and 123 mg/L.

No fish mortality occurred over the duration of the test, although some behavioural aberration, specifically erratic swimming activity, was observed at concentrations > 16.3 mg/L. The tests results indicate that Camonal is at most slightly toxic to the zebra fish with a

96 hour NOEC between 16.3 and 31.4 mg/L. The data indicate that the LC<sub>50</sub> (96 h) > 68.4 mg/L for this species.

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 ±1°C. Five solutions of the chemical with (geometric mean) measured concentrations of 5.3, 10, 20, 35 and 52 mg/L were tested, together with one control. Solution analysis (gas chromatography) for the test compound was conducted daily on samples of both old and fresh test media. Five juvenile daphnia were tested at each concentration, with four replicate tests conducted at each concentration. During these tests the pH of the test solutions was always between 7.4 and 7.8, while dissolved oxygen levels were between 7.9 and 8.9 mg/L and hardness, measured as CaCO<sub>3</sub>, was around 235 mg/L.

No reduction in daphnia mobility was observed during the tests, and the tests results indicate that Camonal is at most slightly toxic to daphnia with a 48 hour EC<sub>50</sub> of > 52 mg/L.

A test on the inhibition of algal growth was also conducted on *Scenedesmus subspicatus* over a 72 hour incubation period at 24°C with (geometric mean) measured concentrations for the test material of 3.2, 6.0, 12, 22 and 42 mg/L (nominal 10, 18, 32, 56 and 100 mg/L, respectively) together with a control containing no chemical. The solutions were made up in distilled water, and the measured test concentrations were between 37 and 50% of nominal concentration at 0 hours, and between 24 and 39% nominal after 72 hours which indicates appreciable adsorption of the test material by the algal mass. The results show the new chemical is at most slightly toxic to this species of green algae, with NOEC (72 h) > 42 mg/L.

The QASR calculations of the ASTER database (US Environment Protection Agency, 1998) also furnished predicted acute toxicity LC<sub>50</sub> data for several fish species which included Rainbow trout (44.5 mg/L), Fathead minnow (100.3 mg/L), Bluegill (76.8 mg/L) and Channel catfish (43.2 mg/L). These calculations also furnished an acute LC<sub>50</sub> of 51 mg/L for immobilisation of daphnia, and a chronic maximum acceptable toxicant concentration (MATC) of 15.2 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 most slightly toxic to aquatic species.

## **11. ASSESSMENT OF ENVIRONMENTAL HAZARD**

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

The ecotoxicity data indicates that the new chemical is at most slightly toxic to the aquatic test species. Based on annual imports of 0.5 tonne, all of which is eventually released to sewer, the daily release on a nationwide basis is 1.36 kg/day. Assuming a national population of 18 million and an average personal contribution of 150 L/day to overall sewage flows, the predicted concentration in sewage effluent on a nationwide basis is estimated as 0.5 µg/L.

When released to receiving waters the concentration is generally understood to be reduced by a further factor of at least 10, so the Predicted Environmental Concentration is around 0.05µg/L. This is several orders of magnitude less than the concentrations at which the compound is likely to demonstrate toxicity to aquatic species.

The chemical is hydrophobic with Log Pow 3.07 which would indicate some affinity for the organic component of soils and sediments. The SimpleTreat and Level 1 Mackay 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 hydroxyl free radicals. Nevertheless, it is likely that some of the chemical would become bound to soils and sediments, and is expected to be slowly degraded to water, carbon dioxide and methane through biological processes. These mechanism 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 above considerations indicate a low hazard to the environment when the new chemical is used as a component of domestic products in the manner indicated by the notifier.

## **12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS**

The notified chemical is of very low acute oral toxicity and low acute dermal toxicity, but is a moderate skin irritant and a slight eye irritant in animals. The main hazards associated with the public and occupational use of the notified chemical will be associated with the irritant properties. Based on liver, thyroid and kidney changes in a 28-day oral study in rats, a NOEL of 150 mg/kg/day was established for the chemical. In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999), the notified chemical is a hazardous substance with risk phrase R38 (Irritating to skin).

The notified chemical will be imported in mixtures as compounded fragrances containing up to 25 % of the notified chemical. The imported fragrances will be classified as hazardous substances when the notified chemical is present at  $\geq 20$  %. The fragrances will be used in the manufacture of consumer products, where the final concentration of the notified chemical will be much lower ( $<1\%$ ).

### *Formulation*

The fragrance mixtures containing Camonal are to be formulated into a variety of consumer products, for example, air fresheners and solid and liquid soaps. The processes will generally be automatically controlled enclosed systems. Dermal exposure to spills and drips on the transfer of the compounded fragrances are likely to be the main route of exposure for formulation workers. This is most likely to occur on connecting and disconnecting the 200 L drums of fragrance, and when cleaning the production equipment and empty drums. Inhalation exposure is also possible, although the vapour pressure of the notified chemical is low. In general, occupational exposure during formulation is expected to be low, and therefore the risk of adverse health effects is low. Adequate ventilation will be provided at

all times, including local exhaust ventilation during filling operations. To protect against possible skin and eye irritation, the workers will wear overalls, safety goggles and gloves.

#### *End-use*

Cleaning workers may be exposed to the notified chemical when using the cleaning products. The concentrations of the notified chemical in the final products are low (<1%). The main exposure route is considered to be dermal. Some inhalation exposure is also possible when the products are formulated as a spray. Exposure and risk for these workers would be higher than that for the general public as the cleaning workers will handle these products on a regular basis, however, due to the low concentration of notified chemical in cleaning product, the risk of adverse health effects due to the notified chemical is low.

Cleaning workers using the products containing the notified chemical should wear gloves when handling these products to protect against possible skin irritancy.

#### *Public health*

As the notified chemical will be used in a wide range of household products there will be widespread public exposure. The notified chemical is a moderate skin irritant and a slight eye irritant in rabbits. However, the hazards associated with skin and eye irritation are likely to be offset by the low concentration of the notified chemical.

In the risk assessment provided by the notifier, the total exposure is estimated to be 0.0011 mg/kg/day. Using the NOEL of 150 mg/kg/day from the repeat dose study, a margin of exposure (MOE) of 136 364 is obtained. Based on this high MOE and the use pattern, it is considered that the notified chemical is unlikely to pose a significant hazard to public health.

### **13. RECOMMENDATIONS**

To minimise occupational exposure to Camonal 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 3765.1 (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;
- A copy of the MSDS should be easily accessible to employees.

#### **14. MATERIAL SAFETY DATA SHEET**

The MSDS for Camonal was provided in a format consistent with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (National Occupational Health and Safety Commission, 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.

#### **16. REFERENCES**

Akhurst L (1996) Camonal: Metaphase chromosome analysis of human lymphocytes cultured in vitro, Project No. KC950463, Huntingdon Life Sciences Ltd, UK.

Allan S (1996) Camonal, Four-week oral toxicity study in the rat with four-week recovery period, Project No. KF950492, Huntingdon Life Sciences Ltd, UK.

Draize JH (1959) Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the US, 49: 2-56.

European Commission (1996a) Technical Guidance Document in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances - PART II.

European Commission (1996b) Technical Guidance Document in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances - PART III.

McRae L (1996a) Acute dermal toxicity to the rat, Project No. KK950461, Huntingdon Life Sciences Ltd, UK.

McRae L (1996b) Acute oral toxicity to the rat, Project No. KO950460, Huntingdon Life Sciences Ltd, UK.

National Occupational Health and Safety Commission (1999) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(1999)]. Canberra, Australian Government Publishing Service.

National Occupational Health and Safety Commission (1994) National Code of Practice for the Preparation of Material Safety Data Sheets [NOHSC:2011(1994)]. Canberra, Australian Government Publishing Service.

OECD (1992) OECD Environmental Monographs No. 61, "The Rate of Photochemical Transformation of Gaseous Organic Compounds in Air Under Tropospheric Conditions". Paris.

Organisation for Economic Co-operation and Development (1995-1996) OECD Guidelines for the Testing of Chemicals on CD-Rom. Paris, OECD.

Parcell B (1996a) Eye irritation to the rabbit, Project No. KW950457, Huntingdon Life Sciences Ltd, UK.

Parcell B (1996b) Skin irritation to the rabbit, Project No. KN950456, Huntingdon Life Sciences Ltd, UK.

Selbie L & Lea L (1996) Skin sensitization study in guinea pigs, Project No. SM950459, Environmental Safety Laboratory, Unilever Research, UK.

Standards Australia (1987) Australian Standard 2919-1987, Industrial Clothing. Sydney, Standards Association of Australia.

Standards Australia (1990) Australian Standard 3765.1-1990, Clothing for Protection against Hazardous Chemicals Part 1 Protection against General or Specific Chemicals. Sydney, Standards Association of Australia.

Standards Australia (1994) Australian Standard 1336-1994, Eye protection in the Industrial Environment. Sydney, Standards Association of Australia.

Standards Australia/Standards New Zealand (1992) Australian/New Zealand Standard 1337-1992, Eye Protectors for Industrial Applications. Sydney/Wellington, Standards Association of Australia/Standards Association of New Zealand.

Standards Australia/Standards New Zealand (1994) Australian/New Zealand Standard 2210-1994, Occupational Protective Footwear. Sydney/Wellington, Standards Association of Australia/Standards Association of New Zealand.

Standards Australia/Standards New Zealand (1998) AS/NZS 2161.2:1998 Occupational protective gloves, Part 2: General requirements, Standards Australia/Standards New Zealand.

US Environment Protection Agency (1998) ASTER Ecotoxicity profile: 2-isobutyl-5-methyl 1,3-dioxane - [CAS No 166301-22-0].

Windebank S & Fedyk J (1996) Camonal: Mutagenicity study in Salmonella typhimurium, Project No. AT950458, Environmental Safety Laboratory, Unilever Research, UK.

## Attachment 1

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

<i>Erythema Formation</i>	<i>Rating</i>	<i>Oedema Formation</i>	<i>Rating</i>
No erythema	0	No oedema	0
perceptible)	1	Very slight erythema (barely perceptible)	1
Well-defined erythema	2	Very slight oedema (barely perceptible)	1
		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*

<i>Opacity</i>	<i>Rating</i>	<i>Area of Cornea involved</i>	<i>Rating</i>
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*

<i>Redness</i>	<i>Rating</i>	<i>Chemosis</i>	<i>Rating</i>	<i>Discharge</i>	<i>Rating</i>
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.		
Diffuse beefy red	3 severe	Swelling with lids half-closed to completely closed	4 severe	Discharge with moistening of lids and hairs and considerable area around eye	3 severe

### *IRIS*

<i>Values</i>	<i>Rating</i>
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