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July 1999

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Questamide H

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

Questamide H

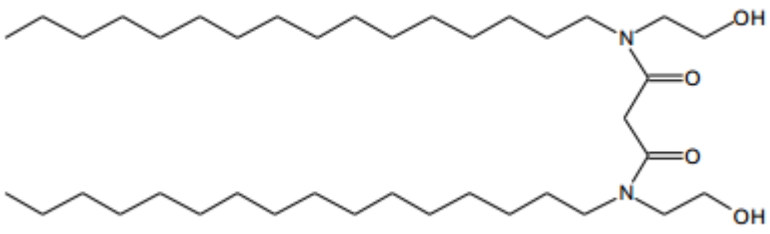
1. APPLICANT

Quest International Australia Pty Ltd of 6 Britton St SMITHFIELD NSW 2164 has submitted a standard notification statement in support of their application for an assessment certificate for Questamide H and has not applied for any information relating to Questamide H to be exempt from publication in the Full Public and Summary Reports.

2. IDENTITY OF THE CHEMICAL

Chemical Name:	propanediamide, N,N-dihexadecyl-N,N-bis-(2-hydroxyethyl)-
Chemical Abstracts Service (CAS) Registry No.:	149591-38-8
Other Names:	bis-hydroxyethyl bis-cetyl malonamide
Trade Name:	Questamide H, Pseudoceramide H
Molecular Formula:	$C_{39}H_{78}N_2O_4$

Structural Formula:



Molecular Weight:	638
Spectral Data:	infrared, ultraviolet/visual and nuclear magnetic resonance (NMR) spectra used to confirm the chemical structure were supplied

Method of Detection and Determination:	identification by NMR spectroscopy and purity by gel permeation chromatography

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	white to slightly yellow waxy solid
Melting Point:	75°C
Density:	1 060 kg/m^3 at 20°C
Vapour Pressure:	5.1 x 10^{-4} kPa at 25°C
Particle Size:	the notifier states that the mean particle size is 10.25 μm with a range of 1 – 100 μm
Water Solubility:	< 1 mg/L at 20°C
Partition Co-efficient (n-octanol/water):	–2.2 < log Pow < 11.5
Hydrolysis as a Function of pH:	not determined - see comment below
Adsorption/Desorption:	not determined - see comment below
Dissociation Constant:	not determined - see comment below
Flash Point:	not determined
Henry's Law Constant:	325.4 Pa.m^3/mol - see notes below.
Flammability Limits:	the test substance could not be ignited with a flame but melted in contact with the ignition source
Autoignition Temperature:	not auto-flammable (up to 400°C)
Explosive Properties:	not determined; notifier states that experience with this and materials of a similar structure indicate no explosive properties
Reactivity/Stability:	stable; notifier states that contact with strong acid, alkali and oxidising agents should be avoided decomposes above 235°C

Comments on Physico-Chemical Properties

All tests were performed according to OECD principles of Good Laboratory Practice. Full test reports were submitted for all properties except particle size distribution.

According to the measured vapour pressure, the chemical has moderate volatility using the scale of Mensinck (Mensinck, 1995).

Water solubility was tested by the flask method (OECD TG 105). The test substance (4.85 mg) was stirred in distilled water (500 mL) at room temperature for 51 h. After the stirring period, the mixture was observed to contain undissolved test substance. Hence, the solubility is less than 1 mg/L.

The Henry's Law Constant was calculated by the notifier according to the method described by Mackay and Wolkoff (Mackay & Wolkoff, 1973) using the following equation: H = MW(g/mole) × Vapour Pressure (Pa)/Water solubility (g/L). The water solubility value used was 1 mg/L, and consequently the calculated Henry's Law Constant will be a minimum value since water solubility is < 1 mg/L.

Determination of the partition coefficient was attempted using three methods.

- An estimation using solubility measurements (OECD TG 107) could not be completed since the solubility of Questamide H in both n-octanol and water is too low.

- The low solubility of the chemical meant that the HPLC method (OECD TG 117) could not be used, since a concentration of Questamide H high enough to be detected would precipitate onto the column. It was determined that the test substance contains an impurity with log Pow < 0.3.

- A theoretical calculation based on the structural formula. Using the Rekker method, the log Pow was calculated to be 11.5. However, since this calculation does not take into account the 3-dimensional structure, it is claimed that the actual Pow is probably lower. If the long chain alkyl groups are substituted by methyl groups then the calculated log Pow is –2.2. Hence, the notifier concluded that the log Pow is between –2.2 and 11.5.

It is accepted that accurate estimation is difficult, but the high aliphatic hydrocarbon content of the new chemical is expected to confer high hydrophobicity on the compound, and a high value of log K_{ow} could be expected.

No data on the potential for adsorption/desorption to soils was provided, but due to the expected high value for log K_{ow}, it is likely that value for log K_{oc} would also be large (Lyman, Rheel & Rosenblatt, 1982). Thus, the compound is expected to have an affinity for the organic component of soils and sediments.

Results for abiotic hydrolysis were not determined by the notifier since the low water solubility substance meant that the concentrations involved were at the limit of detection of the instrumentation.

The polymer contains two amide linkages which could be expected to undergo hydrolysis under extreme pH conditions. However, this is unlikely in the usual environmental pH range where 4 < pH < 9. The low water solubility will also decrease the likelihood for hydrolysis since the predominantly hydrophobic character of the molecule would exclude water from the vicinity of the susceptible amide linkages.
The new chemical contains no acidic or basic functionalities, and so dissociation constant data are not relevant.

4. PURITY OF THE CHEMICAL

Degree of Purity:	> 99%
Toxic or Hazardous Impurities:	none
Non-hazardous Impurities (> 1% by weight):	the notifier states that an isomer of the notified chemical is present at less than 1%
Additives/Adjuvants:	none

5. USE, VOLUME AND FORMULATION

The notified chemical is to be used at less than 1% as a skin conditioning agent in skin creams, shampoos and conditioners. It will be imported in pure form at a rate of up to 250 kgs per year for the first five years, and formulated into end use products.

6. OCCUPATIONAL EXPOSURE

The notified chemical will be imported in 10 or 25 kg steel kegs with a double polyethylene liner. The kegs will be stored at the notifier's premises before being shipped to cosmetic product manufacturers. During transport or storage of drums containing the notified chemical occupational exposure may occur in the event of accidental spillage.

The notifier was able to provide only basic and general information on the notified chemical, as customers are yet to be identified. Closed systems will be used for cosmetic compounding and filling of the cosmetics into containers. Production runs are anticipated to be either of a duration of 1 week, up to 4 times per year or 1 – 2 days per month. Typically less than 6 workers are employed for compounding as the processes are stated to be highly automated. Workers may be exposed to chemical powder during removal from the drums in which it is imported, during weighing and addition to mixing vessels. The notifier states that the formulators would adhere to the GMP standards of the cosmetic industry, and that workers

will wear the protective clothing specified on the Material Safety Data Sheet (MSDS). The MSDS states that the chemical should be handled in well ventilated areas. Workers are to wear gloves, eye protection and protective clothing. The chemical is compounded into cosmetics at less than 1%. The notifier has not provided any details on the use of products containing the notified chemical in the workplace, i.e. in beauty parlours or hairdressing salons. However, there is potential for inhalation exposure to dust and to dermal and ocular exposure.

7. PUBLIC EXPOSURE

The notified chemical will enter the public domain as cosmetic products at a low concentration (up to 1%). Although the public will make dermal and possibly eye contact (eg. while using shampoos containing the notified chemical) with these products, exposure is likely to be low because of the low concentration of the notified chemical in the products.

The potential for public exposure to the notified chemical during transport, reformulation and from disposal is assessed as minimal.

8. ENVIRONMENTAL EXPOSURE

Release

Release to the environment at the various cosmetic production sites should be low and will only arise when equipment is cleaned. The notifier indicated that up to 1% of the chemical may remain in the production equipment after each batch of cosmetic preparation is manufactured and packaged for sale, and this would be washed with other waste into the sewer system. Based on an annual import of 250 kg, this amounts to an annual release of 2.5 kg from activities associated with the manufacture of cosmetic products.

Some residual (unused) product is likely to remain in the empty bottles of cosmetics after use. Again, the notifier estimates that around 1% (annually 2.5 kg) of the new chemical may remain in the packaging after product use. This is likely to be discarded with the empty container with domestic garbage, and would probably be placed into landfill.

The most significant release of the chemical to the environment will come from the cosmetic products being washed from the hair and skin by the general consumer. The bulk of this release is likely to be into the sewer system, and this is estimated to comprise 98% of the total imports of chemical, which amounts to around 245 kg per annum.

Fate

All the new chemical will eventually be released into the environment, and the majority could be expected to be discharged into sewerage systems. The bulk of the chemical will be rinsed into the sewer with wastewater. Due to the expected high value of log K_{oc} (see physico-chemical properties above), once the chemical has entered the sewer system it is very likely to become assimilated with the organic component of sewer sediments, or become associated with suspended particulate matter in the sewerage. Using the calculated Henry's Law Constant and correlation tables (European Economic Community, 1996) for the fate of chemicals that are not biodegradable, the notifier estimated the chemical will partition to air (1%), water (7%) and sludge (92%).

Any chemical that binds to the sludge during the waste treatment process would be disposed of through landfill. Once sludge or container residue is placed in landfill chemical leaching is not expected because of the low water solubility and expected high binding potential to soil. Residues that persist after sewage treatment will enter marine or freshwater environments (from city and country wastewater treatment systems, respectively) in suspension. The concentrations are expected to be very low because of the very high fixation rate in the initial process, the expected movement to sediment/sludge and the high dilution rates in the release processes (see section 11).

In the event of accidental spillage of the chemical into waterways, it is expected that the chemical would bind to and become associated with the organic component of sediments. If the chemical is spilt on land, either during usage or as a result of transport accidents, it is expected to become immobilised in the soil layer. Contaminated soil can then be collected and disposed to landfill.

Biodegradation

A CO_2 Evolution Test (modified Sturm test, OECD TG 301) was performed with Questamide H to determine the degree of ready biodegradability. At ~ 41.5 mg per 2 litres, corresponding to 15 mg total organic carbon/L, the theoretical CO_2 production was estimated to be 2.7 mg CO_2/mg. The relative degradation values calculated from the measurements performed during the test period revealed that it degraded by approximately 5% in 28 days, which was not significant. Since Questamide H is insoluble in water, the lack of microbial degradation could be a consequence of its limited availability for micro-organisms. The study also indicated that Questamide H was non-inhibitory and the EC_{50} value after three hours was > 1000 mg/L. In conclusion, Questamide H was not readily biodegradable under the conditions of the Sturm test as performed.

Bioaccumulation

The low water solubility, low rate of biodegradation and anticipated high values for Log Kow and log K_{oc} suggest potential for bioaccumulation (Connell, 1990). However, the low level and diffuse nature for release of the notified chemical should limit the extent of any bioaccumulation.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Summary of the acute toxicity of Questamide H

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} > 2 000 mg/kg	(Jackson & Ogilvie, 1993c)
acute dermal toxicity	rat	LD_{50} > 2 000 mg/kg	(Jackson & Ogilvie, 1994)
skin irritation	rabbit	non-irritant	(Jackson & Ogilvie, 1993a)
eye irritation	rabbit	slight to moderate irritant	(Jackson & Ogilvie, 1993b)
skin sensitisation	guinea pig	non-sensitiser	(Selbie & Hartop, 1993)

9.1.1 Oral Toxicity (Jackson & Ogilvie, 1993c)

Species/strain:	rat/SD
Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	gavage in propylene glycol
Clinical observations:	none
Mortality:	none
Morphological findings:	none
Test method:	OECD TG 401
LD_{50}:	> 2 000 mg/kg
Result:	the notified chemical was of very low acute oral toxicity in rats

9.1.2 Dermal Toxicity (Jackson & Ogilvie, 1994)

Species/strain:	rat/SD
Number/sex of animals:	5/sex
Observation period:	14 days
Method of administration:	24 hours under occlusive dressing moistened with distilled water
Clinical observations:	none; also no skin irritation observed at any time point
Mortality:	none
Morphological findings:	none
Test method:	OECD TG 402
LD_{50}:	> 2 000 mg/kg
Result:	the notified chemical was of low acute dermal toxicity in rats

9.1.3 Inhalation Toxicity

Not tested.

9.1.4 Skin Irritation (Jackson & Ogilvie, 1993a)

Species/strain:	rabbit/New Zealand White
Number/sex of animals:	3/male
Observation period:	72 hours
Method of administration:	0.5 g of the notified chemical moistened with distilled water under semi-occlusive dressing for 4 hours
Test method:	OECD TG 404
Comments:	no erythema or oedema was observed in any animal at 1, 24, 48 or 72 hours after dressing removal; all Draize scores were zero

Result: the notified chemical was not a skin irritant in rabbits

9.1.5 Eye Irritation (Jackson & Ogilvie, 1993b)

Species/strain: rabbit/New Zealand White

Number/sex of animals: 3/male

Observation period: 6 days

Method of administration: 0.1 g of the notified chemical into the conjunctival sac of the right eye of each rabbit

Draize[a] scores (Draize, 1959):

Cornea	no corneal effects (all Draize scores zero) except for dulling of corneal lustre in animal #1 and #2 at 1 hour, animals #1 and #3 at 48 hours and animal #3 at 72 hours
Iris	slight iridal effects (Draize score of 1) up to and including 72 hours in all animals except that animal #2 had no iridal effects at 72 hours but constriction of the pupil; no effects on days 4 - 6

	Time after instillation																				
Animal	***1 hour***			***1 day***			***2 days***			***3 days***			***4 days***			***5 days***			***6 days***		
Conjunctiva	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***	***r***	***c***	***d***
1	2	2	s	1	2	t	1	1	t	1	0	m	1	0	0	1	0	0	0	0	0
2	2	1	t	2	2	t	1	1	m	1	1	0	1	0	0	1	0	0	0	0	0
3	1	2	t	2	1	t	2	1	t	1	1	s	1	0	0	0	0	0	0	0	0

[a] see Attachment 1 for Draize scales
r = redness c = chemosis d = discharge, s = slight, m = moderate, t = thick

Test method: OECD TG 405

Result: the notified chemical was a moderate eye irritant in rabbits

9.1.6 Skin Sensitisation (Selbie & Hartop, 1993)

Species/strain: guinea pig/Dunkin-Hartley

Number of animals: 20 test (10/sex), 10 control (5/sex)

Induction procedure: 3 pairs of intradermal injections (0.1 mL/site) in the scapular area as follows:

- 1:1 (w/w) of Freund's Complete Adjuvant (FCA) containing 0.01% dodecylbenzene sulphonate/0.9% physiological saline;
- 1.0% notified chemical in 6% acetone/20% polyethylene glycol 400/0.01% dodecylbenzene sulphonate/0.9% physiological saline;
- 1:1 (w/w) mixture of the notified chemical in 6% acetone/20% polyethylene glycol 400/0.01% dodecylbenzene/0.9% physiological saline with FCA to a final concentration of 1.0%

on day 8 the above scapular area was treated with a 2 cm by 4 cm filter paper patch saturated with 25% of the notified chemical in 70% acetone/30% polyethylene glycol 400 under occlusive dressing for 48 hours;

Challenge procedure: 14 days after application of the induction patch an occluded 8 mm diameter filter paper patch saturated with 5% notified chemical in 70% acetone/30% polyethylene glycol 400 was placed on one flank of each test animal for 24 hours

Challenge outcome:

	Test animals		***Control animals***	
Challenge concentration	***24 hours****	***48 hours****	***24 hours***	***48 hours***
5%	0/19**	0/19	0/10	0/10

* time after patch removal
** number of animals exhibiting positive response (one test animal was sacrificed as a result of neck lesions)

Test method:	OECD TG 406
Result:	the notified chemical was a not a skin sensitiser in guinea pigs

9.2 Repeated Dose Toxicity (Lea & Spurgeon, 1994)

Species/strain:	rat/SD
Number/sex of animals:	5/sex/dose group
Method of administration:	gavage in corn oil
Dose/Study duration::	0, 15, 150 or 1 000 mg/kg/day (control, low, mid or high doses, respectively) for 28 days
Clinical observations:	no deaths occurred during the study; non-treatment-related nasal and/or ocular discharge was observed in all groups; no treatment-related changes in body weight at week 4 or in body weight gain were observed during the study

Clinical chemistry/Haematology

Haematology: no statistically significant differences between control and treatment groups

Clinical chemistry: 7% increase in magnesium levels in high dose males; 10% increase in aspartate transaminase, 68% increase in alanine transaminase, 32% increase in alkaline phosphatase levels in high dose males

Macroscopic findings:

no statistically significant differences in organ weights were observed; moderate fluid distension of the uterus was observed in 1 mid dose and 4 high dose females; enlargement of the mesenteric lymph nodes was observed in 1 high dose male

Histopathology:

ovaries: apoptosis in the *corpora lutea* was observed in 4 high dose rats and one mid dose rat; prominent vacuolated cells, possibly macrophages were present in the centre of the *corpora lutea*

uterus: the rats found to have apoptosis in the *corpora lutea* also had pronounced dilatation of the uterine lumen; three of the high dose rats also had prominent keratinisation of the cervical epithelium

one mid dose and one low dose rat were found to have luminal dilatation of the uterus, but this was less pronounced than the uterine changes identified as treatment-related; the incidence and degree of dilatation was considered to be within the normal physiological range, and therefore not due to treatment

mesenteric lymph nodes: histiocytosis was present in the lymph nodes of high dose males and females; the medullary cords of all female rats and 3 male rats were affected as was the paracortex of 2 males and females; histiocytosis was observed also in the sinuses of a number of rats from all treatment groups but the severity was increased in high dose animals
liver: focal hepatocyte necrosis was observed in 3 female and one high dose male rat; an increase in the incidence of parenchymal mononuclear cells was noted in high dose females

spleen: a slight increase in extramedullary haemopoiesis was observed in high dose male and female rats; in view of this observation, a proportion of bone marrow smears from animals in this group and the control group were examined; no abnormalities were detected and smears from the two groups appeared similar; as the increase in splenic extramedullary haemopoiesis was marginal, within the normal background range and not supported by any alterations in haematology parameters or bone marrow smear morphology, it was judged not to be of any toxicological importance.

a variety of spontaneous changes were recorded in animals from all dose groups with no evidence of a treatment-related distribution; the findings were within the spectrum of spontaneous lesions commonly encountered in laboratory rats of this age and strain and were considered by the study authors to be unrelated to administration of the notified chemical

Test method: similar to OECD TG 407

Comments:

the microscopic changes observed in the ovaries and uterus were judged to be consistent with, but more pronounced than the normal cyclic changes that occur during the pro-oestrus to oestrus stages of the rat oestrus cycle, apoptosis of luteal cells being a common feature of the ovary during oestrus; the incidence and severity of the genital tract changes increased with dose and were considered to be a direct toxic effect of the notified chemical or due to a hormonal imbalance resulting in an exaggeration of the normal changes that occur in the ovary in the course of the oestrus cycle

the hepatocyte necrosis noted in three high dose females and one high dose male rat comprised only a few discrete foci with no predilection for any particular region of the liver lobule and was considered to be unlike xenobiotic-induced cytotoxic hepatocyte necrosis which generally has a more specific distribution within the liver lobule and is usually more widespread; the effect on the liver of female rats was more severe than in males and an increase in parenchymal mononuclear cells was noted also in the majority of high dose female rats; there was, however, no increase in liver weight and the plasma activities of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were only significantly increased in male rats; it was concluded that the pattern of hepatocyte necrosis seen in this study, which is occasionally noted in untreated control rats and has been attributed to pathological organisms arriving from the intestines via the portal blood supply, represented a treatment-related exacerbation of a spontaneous change rather than a direct toxic effect (although no such lesions were seen in control animals)

accumulation of histiocytes in the mesenteric lymph nodes is a common response to the oral administration of xenobiotics; there was no evidence of any degenerative effect associated with these histiocytes; the enlarged mesenteric lymph nodes noted at necropsy in one high dose male animal were considered to be consistent with this microscopic finding.

genital tract and liver changes similar to those seen after treatment with the notified chemical can occur in control animals; it was considered to be possible that a chance imbalanced incidence of these background findings resulted in an apparently treatment-related distribution, a problem exacerbated by the small group size and known to occur in tissues such as the genital tract which undergo cyclic changes

Result: the NOEL for the notified chemical was judged to be 15 mg/kg/day with target organs being the ovary, uterus, liver and mesenteric lymph node; effects at 150 mg/kg/day were limited to the ovary and uterus

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* Reverse Mutation Assay (Bourner et al., 1993)

Strains:	TA 1535, TA 1537, TA 98, TA 100
Concentration range:	0.5, 5, 50, 500, 5 000 µg/plate
Test method:	EC Method B 14 (similar to OECD TG 471)
Comments:	the notified chemical was toxic at the top dose as judged by lack of effect on microcolony formation; precipitation above 500 µg/plate was predicted to obscure scoring of mutants and some precipitation was seen at this dose; positive control mutagens, which established the sensitivity of the assay were: 2-aminoanthracene: +S9; 2-nitrofluorene: TA 98 –S9; sodium azide: TA 1535 and TA 100 –S9; 9-aminoacridine: TA 1537 –S9
Result:	the notified chemical was not mutagenic at doses up to 500 µg/plate in bacteria in either the absence or presence of metabolic activation provided by Aroclor 1254-induced SD rat liver S9 fraction

9.3.2 *In vitro* Cytogenetic Study in Human Lymphocytes (Beard et al., 1993)

Cells:	phytohaemagglutinin-stimulated human peripheral lymphocytes from female donors
Doses:	500 µg/mL for approximately 19 or 43 hours in the absence of metabolic activation provided Aroclor 1254-induced rat liver S9 fraction (S9) and in its presence for 3 hours
Test method:	similar to OECD TG 473
Comments:	the dose level was chosen to reduce the mitotic index to 40 – 80% of controls; negative controls were within the expected limits; the positive control substances were ethylmethane sulphonate (500 µg/mL) or cyclophosphamide (12.5 µg/mL) and demonstrated the sensitivity of the assay

Result:	chromosomal aberrations were not induced under the conditions of this assay in either the absence or presence of metabolic activation provided by rat liver S9 fraction

9.4 Developmental toxicity

9.4.1 Preliminary screening study of developmental toxicity and teratogenicity (Spurgeon et al., 1995)

Species/strain:	rat/SD
Number/sex of animals:	20 test females; 20 control females
Method of administration:	gavage in corn oil

Dose/Study duration:

0, 1 000 mg/kg/day for 28 days followed by necropsy of half of the females on day 29 and mating of the other half and continued dosing until gestation day 19; on day 20 females were killed and examined for maternal, foetal and reproductive parameters

Clinical observations:

no decedents and no treatment-related clinical signs; body weight and body weight gain were not affected by treatment; no effect on oestrus cycle; pregnancy rate was 90% in the treated group and 100% in the control group

Reproduction and foetal parameters:

uteri of the treated group were normal and there was no treatment-related effect on deaths as a percentage of implantations, percentage of late foetal deaths, number of *corpora lutea*, implantations or live foetuses, numbers of live male and female foetuses and sex ratio, pre- and post-implantation losses and foetal weight

Macroscopic findings:

for rats killed after 28 days of dosing, one treated rat had enlarged mesenteric lymph nodes and another rat had a few pale foci on the liver

for rats killed on gestation day 20 there were no treatment-related findings

abdominal fat deposition was similar in treated and control rats

Histopathology:

rats killed following 28 days of dosing

treatment-related findings in the ovary, liver and mesenteric lymph node were observed

ovaries: vacuolated cells were present in the *corpora lutea* of 6/10 treated rats; granulomata were present in the *corpora lutea* of 4/10 treated rats; in total, 9/10 rats showed a histological change in the ovary

liver: granulomata in the liver of a single treated rat corresponding with the pale foci noted macroscopically in this animal; for this reason the tissue was processed as an abnormality

mesenteric lymph node: marked histiocytosis in the mesenteric lymph node of a single treated rat, corresponding with the enlargement noted macroscopically

incidental findings: there was a higher incidence of luminal dilatation of the uterus in treated, but this was consistent with the stage of the oestrous cycle that they were in and is not considered likely to be related to treatment; treated rats were in a variety of different stages of the oestrous cycle, such as would normally be expected in rats of this age

rats killed on day 20 of gestation

ovaries: there were vacuolated cells in the *corpora lutea* and granulomata in the ovaries of the majority of treated rats

liver: there were granulomata in the livers of two treated rats (these livers were processed due to the presence of macroscopic abnormalities).

all other findings were of a nature and incidence commonly found in rats of this age and strain, and were considered of no toxicological importance; there were no histological findings in tissues from the pair of rats that did not breed successfully to suggest any infertility

Foetal observations:

external observations
at dissection, narrow and flattened heads were seen in 15/113 foetuses from 7/9 litters treated with the notified chemical; 27/113 treated foetuses were observed to have narrow heads and 13/113 flattened heads; this finding was not seen in the 125 control

foetuses; the incidence was significantly higher in the treated foetuses and occurred throughout the range of litter sizes and range of foetal weights, it was not associated with either large or small litters, or heavy or lighter foetuses; the appearance of narrow/flattened heads was different from that of domed heads, often associated with smaller foetuses, seen in both control and treated foetuses

there was no significant difference in fixed weights

visceral observations
a range of findings was observed on visceral examination of the fixed foetuses; no significant differences in the incidence of these findings were observed

skeletal examination
there were no noticeable differences between the treatment and control groups with respect to the number of morphological changes or in the degree ossification and in particular no structural deviations in the skull bones that might underlie the finding of narrow/flattened heads at necropsy

examination of thick slices of heads
heads of a proportion of affected foetuses plus unaffected foetuses from the same litters and also control foetuses were sectioned and assessed; examination of intact heads or heads after freehand serial slicing did not reveal any differences between treated or control foetuses or any structural abnormalities

Test method:

similar to OECD TG 414

Comments:

there was no indication of a treatment-related effect on hormone levels, particularly follicle stimulating hormone, a marker of ovarian toxicity

the only treatment-related finding in the foetus was the observation of slightly narrowed/flattened heads in some treated foetuses at caesarean section; other external and visceral findings did not appear to show a treatment related incidence and were judged to be spontaneous; on examination of skeletons and thick sections of heads no structural abnormalities or morphological changes in soft tissue or cranial bones were found; the view of the pathologists was that the narrow and flattened appearance of the head was not a structural defect, but may have been due to compression of the foetus in the uterus, a physiological/ pharmacological effect; it was considered to be a slight effect, because there were no other signs of uterine compression, such as wavy ribs or limb flexures in the foetuses

there was no indication that treatment had adverse effects on the oestrous cycle, mating, caused maternal toxicity, embryolethality or structural abnormalities in

foetuses; while slight changes in head shape were observed at caesarean section, the no effect level for which could not be determined, these changes were considered not to be a structural defect;

administration of the notified chemical elicited microscopic changes in the ovaries, liver and mesenteric lymph node as noted in a previous 28-day oral toxicity study (see section 9.2)

vacuolated cells in the *corpora lutea* were judged to represent macrophages

granulomata were present in the *corpora lutea* of rats at 28 days; in rats killed on day 20 of pregnancy granulomata were still present and better defined, but their location was less clearly evident; use of a reticulin stain showed that the granulomata were walled off by reticulin fibres in a circular pattern, suggesting that they were inside old *corpora lutea*; control rats killed on day 20 of gestation generally had only large *corpora lutea* of pregnancy present in their ovaries; the corresponding treated rats however also had these smaller granulomatous structures present, suggesting persistence of older generations of *corpora lutea*

vacuolated cells in the ovaries and the histiocytes in the mesenteric lymph node were considered to contain endogenous lipid material, the notified chemical or its metabolite; the changes in the liver, ovaries and mesenteric lymph nodes were considered to involve histiocytes (macrophages) and to share a common aetiology; the granulomata in some livers were associated with occasional necrotic hepatocytes; granulomata have been described in the liver following administration of certain types of liposomes and accumulation of histiocytes in the mesenteric lymph nodes have been described following administration of xenobiotics in the diet

if the incidence of microscopic changes in the 28-day dose group is compared with that in the rats killed on gestation day 20 (which had received at least 48 days dosing), effects on the ovary appear more frequently in the latter; granuloma(ta) in the ovary and limited numbers of livers examined were observed in this study but not in the previous 28-day oral toxicity study (see section 9.2)

Result:

it was concluded that the notified chemical administered to rats by gavage for 28 days, or for an additional period up to day 20 of gestation, produced some morphological changes in the ovary, liver and mesenteric lymph node, but had no effect of fertility, hormone levels or the oestrus cycle and was not maternotoxic; slight differences in the appearance of the head were seen in some treated foetuses on day 20 of gestation but no structural abnormalities were observed

9.4.2 Developmental toxicity and teratogenicity in rats: full study (Twomey, 1998)

Species/strain:	rat/SD
Number/sex of animals:	10 test females/dose; 10 control females
Method of administration:	gavage in corn oil
Dose/Study duration::	0, 15, 150 or 1 000 mg/kg/day from gestation day 6 to 17 inclusive
Clinical observations:	no premature deaths or treatment-related clinical signs; no effect of treatment on maternal bodyweights or food consumption

Reproduction and foetal parameters:

all females in the control and mid dose groups and 9/10 females in the other groups became pregnant

no effect of treatment was observed on the numbers of *corpora lutea*, implantations or live foetuses or pre- or post-implantation losses; although pre-implantation losses in the high dose group were higher than in the other groups, they were considered to be unrelated to treatment because implantation generally occurs before day 6 of pregnancy (the first day of dosing)

the foetal sex ratio was unaffected by treatment as were mean foetal and placental weights

there were 1, 0, 1 and 0 foetuses with major abnormalities observed in the control, low, mid and high dose groups, respectively; for the foetus in the control group, the abnormalities observed were the absence of one or more thoracic centra and thoracic neural arch and major fusion of the ribs; for the foetus in the mid dose group, the abnormality observed was an interrupted aortic arch; due to the low incidence of major foetal abnormalities, the fact that no major abnormalities were observed in the high dose group and that one of these foetuses was in the control group, these abnormalities were considered not to be related to treatment

there was no effect of treatment on the overall incidences of minor foetal abnormalities or variations

the only minor skeletal abnormality observed with a statistically significant trend was incomplete ossification of the sacral neural arches; however, there was no statistical difference between the treatment groups and the control; in the mid and high dose groups, the observation of one skeletal variation - non-ossification of the hyoid bone of the skull, was statistically significantly increased in comparison with the control

group; however, although the highest incidences of these findings were at 1 000 mg/kg/day, both were within background range and in the absence of further increased incidences of any similar findings, were considered not to be related to treatment; it should be noted that these findings are considered to be transitory and would be expected to disappear once the pups were born and were weaning

other variations observed that were increased in the treated groups included increased renal pelvic cavitation, dilation of the ureter, incomplete ossification of the interparietals and occipital bones of the skull, vestigial 14th ribs and bilobed thoracic centra; however, all of these findings were within background range and considered not to be related to treatment

Test method: similar to OECD TG 414

Result:

the notified chemical elicited no maternal or foetal developmental toxicity following oral (gavage) administration to pregnant rats during organogenesis at dose levels up to 1 000 mg/kg/day

9.5 Toxicokinetic Data

9.5.1 Toxicokinetics in the Rat after Gavage, Intravenous and Topical Administration (Sanders et al., 1994)

The notified chemical labelled with ^{14}C was administered (by gavage) to male and female rats at a dose of 6 mg/kg. Over 96 hours, virtually the entire administered label was present in the faeces with 0.3% present in urine. It was estimated that 2 – 3% was absorbed from the gastrointestinal tract. Excretion of label in the faeces was very high within the first 24 hours (> 96%). After 96 hours approximately 2% of the label was present in the carcass. No $^{14}CO_2$ was detected in expired air.

The absorbed label accumulated in a number of organs and tissues, particularly the liver, spleen, adrenals and ovaries (females). Lower levels of accumulation were observed in the lungs and bone marrow. Clearance of the label was very slow. There was little metabolism of the notified chemical but degradation was observed after contact with rat faeces in aqueous slurry and dry forms. Three unidentified metabolites were present at low concentrations.

For intravenous administration, 6 male rats were dosed via the tail vein with the notified chemical labelled with ^{14}C in PEG 400. After 1, 2, 4, 8 and 24 hours blood, liver, spleen, kidney, brain and adrenals were assayed for ^{14}C. Following intravenous injection of the notified chemical at 2.6 mg/kg, 2.6% of the dose was excreted within 24 hours equally distributed in faeces and urine. There was no expiration of $^{14}CO_2$. The administered ^{14}C was rapidly cleared from the blood and deposited into the liver, adrenals, spleen and kidneys. Within 1 hour of dosing the liver contained 53% of the

dose and over the following 24 hours the level increased to 89%. The spleen contained 6% to 10% of the dose but a slightly higher concentration per gram of tissue than the liver. The spleen ^{14}C level increased slightly over the first 4 hours before falling back to the 1 hour level by 24 hours. The brain, adrenals and kidneys accounted for very low levels of ^{14}C and the carcass contained 13% of the dose at 24 hours. The label was removed very slowly from the tissues analysed. Whole body autoradiography showed that the bone marrow was also a target organ. Approximately 8% of the ^{14}C in the liver was a possible metabolite.

For study of toxicokinetics after topical application, ^{14}C-labelled notified chemical in acetone was applied to the skin of 4 male rats and occluded for 48 hours. Approximately 0.2% of the applied dose was absorbed through the skin and 0.1% retained in the carcass. Between 7% and 8% of the dose was retained at the site of application and the remainder of the dose was rinsed off. The results suggest considerable penetration into the skin but poor removal via the peripheral blood.

In a second study of toxicokinetics after topical application, ^{14}C-labelled notified chemical in acetone was applied to the skin of 2 female rats followed by 24 hours of occlusion. Approximately 0.01% of the dose was absorbed through the skin and traces levels were found in the urine, faeces and carcass. Blood levels were below the detection limit. The notified chemical was mainly localised in the *stratum corneum* and around the hairs and upper regions of the hair follicles. Very little label was present in the dermis.

9.5.2 Toxicokinetics in the Rat after Multiple Gavage Administration (Sanders et al., 1995a)

The notified chemical labelled with ^{14}C was administered (by gavage) to female rats at a dose of 1 000 mg/kg/day on 3 consecutive days. At time points up to 36 days, animals were killed and selected known target organs were assayed for ^{14}C. ^{14}C levels in urine and faeces were also monitored up to day 36. The distribution of ^{14}C was examined by whole body autoradiography after a single dose and after the three consecutive doses.

Administration of the test material proved very difficult due to high viscosity and only 3 of a planned 8 daily doses were administered. Abnormal bodyweight loss was observed in all rats on the 3 days of dosing and for the first 48 hours of the recovery period. High individual variability of fate and disposition of the test substance observed on days 1 and 2 was judged to be the result of high abnormal stress levels. Faecal production during the 3 days after the first dose was much lower than normal in most rats, and judged to be due to a combination of reduced diet intake, treatment-related stress and the viscous nature of the preparation.

The urine ^{14}C level peaked 48 hours after the final gavage treatment at 1 854 dpm/mL of urine and the faecal ^{14}C level peaked 24 hours after the final gavage treatment at

17.7 x 10^6 dpm/g of dry faeces. After these points the level of ^{14}C in both excreta declined rapidly.

Labelled notified chemical was rapidly taken up by various tissues in small amounts and slowly cleared. Half-lives of clearance from the ovary was between 9 and 16 days, from the liver between 15 and 27 days and from the blood between 19.5 and 25 days. Maximum levels were reached after two gavage treatments for the adrenals (25 520 dpm/g) and blood (796 dpm/g) and on day 5 for the ovary (27 531 dpm/g) and liver (10 241 dpm/g).

9.5.3 Toxicokinetics in the Rat after Topical Application (Sanders et al., 1995b)

This study was conducted in two parts. In the first part groups of four female rats were treated topically with the notified chemical labelled with ^{14}C under occlusive dressing for 48 hours at doses of 0, 0.07, 0.48 or 2.6 mg/cm^2 over an area of 9.6 cm^2 of skin. The chemical vehicle was Petroleum Jelly (vaseline). Approximately 0.02, 0.1 and 0.03% of the applied dose was absorbed, respectively, in the low, mid and high dose groups. The amount remaining within treated skin was 26, 19 and 33% for the low, mid and high dose groups. Unabsorbed material ranged from 63 – 73%. No label could be detected in the brain, liver, ovaries, uterus, kidneys, lungs, femurs, small intestine or adrenals. It was concluded that only very low absorption of the notified chemical occurred after topical application. The ultimate fate of skin residues or unabsorbed chemical at times greater than 48 hours is not known.

In the second part of the study, groups of twenty female rats were treated topically with 0.1 g of the notified chemical labelled with ^{14}C in either a lotion formulation or in Petroleum Jelly (vaseline) under occlusive dressing for 24 hours. After 1, 7, 14 or 28 days rats were killed and the treated site, heart blood, brain, liver, ovaries, uterus, kidneys, lungs, femurs, small intestine (with contents) and adrenals were removed for ^{14}C assay. During the 24 hours of occlusion, the overall level of percutaneous absorption of ^{14}C was 0.1% of the applied dose for both treatment groups. Between 48 and 90% was removed by skin wiping, and approximately 6% (lotion base) and 4% (Petroleum Jelly) remained in the treatment site. During the six days after removal of the device protecting the treatment site, the level of ^{14}C in faeces increased to a peak of 0.5% of the dose on day 4 indicating that further absorption from skin residues occurred after 24 hours. This is supported by measurements in the skin, showing a sharp decline between day 1 and day 7. Urine levels remained fairly constant at approximately 0.02% during the same six days. On days 7, 14 and 28 the overall level of ^{14}C in the tissues remained constant at approximately 0.01% of the dose in the liver and small intestine (with contents) whereas the level in the other organs was below the detection limit. Blood levels of ^{14}C remained very low throughout the course of the experiment. It was concluded that the notified chemical applied to rat skin in either a lotion base or in vaseline was poorly absorbed across the skin.

9.6 Skin Deposition and Absorption

9.6.1 Skin Deposition (Sanders & Howes, 1994)

The levels of deposition of the notified chemical onto pig skin were determined after topical application in a rinse-off toiletry product (shower gel) at a concentration of 0.5%. ^{14}C-labelled notified chemical was applied to isolated whole pig skin at 31 $\mu g/cm^2$ for 5 minutes. Following topical application most, but variable amounts (69 – 85%) was removed with distilled water. Soap solutions (8% soap – shower gel, Unilever No. 2 soap base or Dove soap base) were able to remove between 3.6 and 6.2% and between 1.9 and 4.1% remained on the skin. It was concluded that low levels of the notified chemical would be deposited onto skin from rinse-off skin cleansing systems and the depot formed is fairly resistant to rinsing with water or surfactants.

9.6.2 Skin Absorption (Pendlington et al., 1995)

The *in vitro* percutaneous absorption of the notified was measured using Franz flow-through cells and keratomed pig, human and rat skin and heat separated pig and human skin. The heat separation technique resulted in considerable skin damage. Therefore results from keratomed skin are given. The notified chemical was shown to penetrate skin poorly. The greatest penetration was 1.2% with rat skin, suggested to be related to the higher number of hair follicles. The notified chemical penetrated pig skin to a level of 0.06%. When an aqueous ethanol receptor solution was used with human skin, penetration was 0.04% of the applied dose. When a receptor solution containing bovine serum albumin was used with human skin (a situation closer to the *in vivo* situation), penetration was 0.004%.

9.7 Overall Assessment of Toxicological Data

In toxicokinetic studies, the notified chemical was shown to be absorbed slowly from the gastro-intestinal tract and across human, rat and pig skin. In human skin, penetration was shown to be a maximum of 0.04% of the absorbed dose. In the gavage studies the major route of elimination was in the faeces. However, following absorption, mainly by the adrenals, liver and ovary, clearance was very slow. After intravenous administration, most of the chemical accumulated in the liver and spleen. Following deposition of the notified chemical on skin in a rinse-off cosmetic product, low levels remained but were resistant to removal. There is some evidence that skin residues continue to be absorbed.

The notified chemical was of very low oral toxicity in rats (LD_{50} > 2 000 mg/kg) and low dermal toxicity in rats (LD_{50} > 2 000 mg/kg). It was not a skin irritant in rabbits and not a skin sensitiser in guinea pigs. In an eye irritation study in rabbits, the notified chemical was moderately irritating, with iris effects observed in all animals.

A 28-day oral (gavage) repeated dose study revealed that target organs were the ovary,

uterus, liver and mesenteric lymph node. The NOEL was 15 mg/kg/day, based on fluid distension of the uterus and microscopic changes in the ovaries and uterus at the mid and high doses. In general the target organs were those identified in the toxicokinetic studies as those involved in uptake of the notified chemical.

In a preliminary screening study of developmental toxicity and teratogenicity, the notified chemical was administered to dams for 28 days prior to and during organogenesis, at 1 000 mg/kg/day. Morphological changes to the ovary, liver and mesenteric lymph nodes were observed, however, no significant effects on fertility, hormone levels or the oestrous cycle were apparent. In the treated foetuses, a significantly higher incidence of narrow and flattened heads was observed at dissection on day 20 of gestation, which could not be explained.

In a full study, the notified chemical was not maternotoxic or teratogenic in pregnant rats when administered during organogenesis at dose levels up to 1000 mg/kg/day.

The notified chemical was not an *in vitro* mutagen as judged by negative results in studies of mutagenesis in bacteria and chromosomal aberrations in human peripheral lymphocytes.

From the results of toxicological data provided, the notified chemical is classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999). On the basis of iris effects in the rabbit, the risk phrase 'R36 - Irritating to eyes' is warranted.

In the repeated dose study, the principal target organs were the ovaries and uterus, with morphological changes to the ovaries also observed in a preliminary developmental and teratogenicity study. On this evidence, there is some cause for concern regarding human fertility (category 3) and the risk phrase 'R62 - Possible risk of impaired fertility' is warranted. Although the results of the full developmental toxicity were largely negative, the high incidence of narrow and flattened heads in the preliminary study indicates some cause for concern regarding human developmental toxicity (category 3), so the notified chemical should carry the risk phrase 'R63 - Possible risk of harm to the unborn child'.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

Since the chemical is being used in quantities less than 1 tonne, no ecotoxicological information is required by the Act. However, the following ecotoxicity studies have been supplied by the notifier. The tests were performed in compliance with OECD/EEC Test Methods and according to OECD Principles of Good Laboratory Practices.

Species	*Test*	*Test conc (nominal) mg/L*	*Result*[a]
Carp (*Cyprinus carpio*)	Acute Toxicity (static) (OECD TG 203)	up to 100	96 h LC_{50} > 100 mg/L
Water Flea (*Daphnia magna*)	Acute Toxicity - Immobilisation Test (Static Test) (OECD TG 202)	up to 100	48 h EC_{50} > 100 mg/L
Green Algae (*Scenedesmus subspicatus*)	Growth Inhibition (Static Test) (OECD TG 201)	up to 100	72 h EC_{50} > 100 mg/L
Aerobic Waste-water Bacteria	Activated Sludge Respiration Inhibition (OECD TG 209)	100-1000	3 h EC_{50} > 1000 mg/L

[a]see comments below

Comments on Ecotoxicological Tests

Nominal concentrations up to 100 mg/L were tried in the test method. Precipitation of the test substance was observed at concentrations of 1.0 and 10 mg/L. The low water solubility of Questamide H meant that it was not possible to maintain a stable dispersion at concentrations higher than 1 mg/L.

There was no suitable analytical method available for determination of the actual test substance concentrations in the test solutions. Hence, there could be no confirmation of concentrations at the completion of the tests.

Fish / Aquatic Invertebrates

A Questamide H concentration of 100 mg/L could only be reached using the dispersion agent Cremophor EL to disperse Questamide H, because of its low solubility (< 1 mg/L). The final test solution used for the acute toxicity tests for carp and water flea was a turbid suspension containing undissolved test particles.

Fish showed no visible effects during the 96 hour test period. The notifier concluded the 96 h-LC_{50} for carp exposed to Questamide H was greater than 100 mg/L, the maximum concentration tested and it is concluded that toxic levels of chemical could not be attained because of its low solubility.

Similarly, concentrations acutely toxic for *Daphnia magna* could not be reached because of the low water solubility of the substance. Therefore, the notifier concluded the 48 h EC_{50} for effect on mobility was beyond the maximum solubility of Questamide H in water, *ie.* EC_{50} >100 mg/L.

However, in both cases, the concentration to which organisms were exposed cannot be determined exactly, and it can only be concluded that the substance is not toxic up to the limit of its water solubility.

Algae

Dispersants were not used in this test since they may affect cell growth at concentrations of 0.1 mL/L. Hence, a supersaturated dispersion of 100 mg/L in water was stirred for 96 h then filtered to remove undissolved test substance. Algal suspensions were exposed to 0.1 to 100% of the filtrate. The results indicated that Questamide H inhibited cell growth and reduced growth rate of algae only slightly at concentration levels approaching the maximum solubility of the substance in water. Again, the exact level of exposure cannot be calculated accurately.

Microorganisms

No significant inhibition in sludge respiration rate was recorded at the test concentrations of Questamide H. Therefore, under the conditions used for the test, Questamide H was not toxic to activated sewage sludge microorganisms at a nominal concentration of 1000 mg/L.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

PEC Calculation

The most significant environmental exposure would be from the release of the chemical in the sewer system after washing from the body after use. The Predicted Environmental Concentration (PEC) has been calculated by the notifier using a worst case scenario where all material is discharged to wastewater in one city, based on the following assumptions:

- 98% of the imported chemical (250 kg) is released to the sewer, and spread over 365 days per year. Therefore, the daily release of the chemical will be 671 g.
- Sewer output is based on a city containing 3 million people, averaging 150 L of water per day with a surface water dilution factor of 10.
- No removal through adsorption to material in sewage treatment plants.

On the basis of these assumptions, an approximate PEC of 1.50 µg/L is obtained for city sewage [ie 671x 10^6µg/day/(3x10^6x150 L/day)]. If it is assumed that on release to receiving waters, the effluent is further diluted by a factor of 10, the resultant environmental PEC is 0.15 µg/L.

The above calculation represents an extreme case since it assumes all release is through a single large metropolitan sewer, with no adsorption of the chemical to sludge or particulate matter. As remarked above, it is expected that the chemical will have high affinity for the organic component of soils and sediments, consequently significant removal into sewer sediments could be anticipated. If, as

is likely to be the case, release of the chemical is nationwide, the PEC is significantly smaller than that estimated above.

The calculations show that the exposure to fish, daphnia, algae and wastewater treatment bacteria is at levels unlikely to cause any significant effect. At higher release rates or lower dilutions, there is still unlikely to be any significant effect on these species, since the concentration of the chemical would still be limited by its very low solubility.

In the event of accidental spillage of the chemical on land, either during usage or transport, it is expected that the chemical would become immobilised in the soil layer. Contaminated soil can then be collected and disposed of to landfill. Solid waste consigned to landfill, either from spillage or residues in packaging, would be expected to be immobile in the landfill sites. Movement of the chemical by leaching from landfill sites is not expected due to the low water solubility, and expected high affinity for soils and sediments.

If the chemical is spilt into waterways, it is not expected to disperse into the water, but settle out onto sediments.

The chemical is not readily biodegradable. This suggests a potential for bioaccumulation. However, the low import volumes and therefore low exposure, will reduce the quantity of notified substance eventually released to the aquatic environment and limit the potential for bioaccumulation.

Given the above, environmental exposure and the overall environmental hazard is expected to be low.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The toxicological data supplied show that the notified chemical is not likely to be acutely toxic or genotoxic and is not likely to be a skin irritant or skin sensitiser. It is a moderate eye irritant and is determined to be a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999).

The notified chemical has the potential to exhibit systemic effects (liver, female genital tract) on repeated or prolonged exposure. In the repeated dose oral toxicity study, effects on ovaries and uteri were observed at a dose of 150 mg/kg/day for 28 days. However, the pathologist report suggested that, although these changes were apparently treatment-related, they could be interpreted as a chance imbalance of spontaneous cyclic changes. Therefore, on this basis alone the notified chemical is not determined to be a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission, 1999). However, in a preliminary developmental toxicity range finding study, effects on the ovary were again observed when dams were treated for 28 days prior to and during organogenesis at 1 000 mg/kg/day. Therefore, together with the

results of the 28-day repeated dose toxicity study, the notified chemical is determined to be a hazardous substance in relation to NOHSC criteria as having category 3 effects on fertility. In this same range finding study, a high incidence of narrow and flattened heads in foetuses suggests cause for concern regarding human developmental toxicity (category 3).

The risk phrase R36 – Irritating to eyes should appear on MSDS and labels for products containing the notified chemical at and above a concentration of 20%; the risk phrase R62 – Possible risk of impaired fertility and the risk phrase R63 – Possible risk of harm to the unborn child should appear on MSDS and labels for products containing the notified chemical at and above a concentration of 5%.

Toxicokinetic studies showed that the notified chemical is absorbed slowly from the gastro-intestinal tract and across human, rat and pig skin. Following absorption the chemical accumulated in the adrenals, liver and ovary where clearance was very slow. Uptake of the notified chemical into the liver and ovaries and its slow clearance is likely to account for the observed organ toxicity.

Occupational Health and Safety

The notified chemical will be imported as a powder in pure form. The risk of adverse health effects to workers involved in transport and storage of the notified chemical resulting from accidental release from containers is likely to be low given the sturdy design of the import containers.

The notified chemical will be compounded into cosmetic products to a final concentration of approximately 1%. There is the possibility of exposure and eye irritation while weighing out and adding the notified chemical to mixing vessels. The notifier states that, as customers are yet to be identified, the details of the use of engineering controls and personal protective equipment (PPE) are not known. However, the use of local exhaust ventilation, "clean" rooms, adequate PPE and enclosed mixing vessels and filling areas is typical of the cosmetics industry where there is a strong requirement to adhere to GMP principles. The employer is responsible for maintaining airborne exposure to the notified chemical below the NOHSC inspirable dust exposure standard of 10 mg/m^3 (National Occupational Health and Safety Commission, 1995) as a significant proportion of particles are in the inspirable range (particle size is stated to be 50 μm or less).

Following filling of cosmetic products into containers, the risk to workers is minimal as the concentration of chemical in products is below the concentration cut-offs which would necessitate the products being determined to be hazardous substances under NOHSC criteria.

Public Health

Members of the public will make dermal contact, and possibly eye contact with the notified chemical when using products containing it. Although the notified chemical is a moderate eye irritant, eye irritation is not likely to occur because of the low concentration in cosmetic products. Signs of developmental toxicity were seen in a preliminary reproduction/developmental study in rats, but the effects could not be confirmed in a subsequent developmental study. Moreover, at a low concentration of the notified chemical

in cosmetic products (< 0.1%) and a low rate of dermal absorption of the chemical, exposure to the chemical is likely to be low.

13. MATERIAL SAFETY DATA SHEET

The MSDS for the notified chemical was provided in accordance with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (National Occupational Health and Safety Commission, 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.

14. RECOMMENDATIONS

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

- Goggles, gloves, a face mask and overalls conforming to Australian or Australian/New Zealand Standards should be worn during weighing and transfer of the notified chemical mixing vessels. Goggles should conform to AS 1336 and AS/NZS 1337, gloves should conform to AS/NZS 2161.2, the face mask should conform to AS/NZS 1715 and 1716 and overalls should conform to AS 2919.

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

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

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

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

The following regulatory action is recommended:

- The notified chemical may be recommended to NOHSC for consideration for an exposure standard;

- The notified chemical may be recommended to NOHSC for consideration for inclusion in the NOHSC List of Designated Hazardous Substances.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under subsection 64(1) of the Act, if more reproductive/developmental studies become available, secondary notification of the notified chemical shall be required.

Should import volumes exceed one tonne per annum, more accurate water solubility results will be needed to allow better estimation of likely levels of exposure to aquatic organisms.

Secondary notification of the notified chemical shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise.

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Attachment 1

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

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

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

CORNEA

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

CONJUNCTIVAE

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

IRIS

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