File No: NA/908

September 2001

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Promidium CO

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For enquiries please contact the Administration Section at:

Street Address: 92 -94 Parramatta Rd CAMPERDOWN NSW 2050, AUSTRALIA
Postal Address: GPO Box 58, SYDNEY NSW 2001, AUSTRALIA
Telephone: (61) (02) 9577 9514 FAX (61) (02) 9577 9465

Director
Chemicals Notification and Assessment

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Promidium CO

1. APPLICANT

Uniqema of 14 Woodruff Street, Port Melbourne, Victoria, 3207 has submitted a standard notification statement in support of their application for an assessment certificate for Promidium CO.

2. IDENTITY OF THE CHEMICAL

The chemical name, CAS number, molecular and structural formulae, molecular weight, spectral data, details of the chemical composition and details of exact import volume and customers have been exempted from publication in the Full Public Report and the Summary Report.

Marketing Name: Promidium CO

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C & 101.3 kPa:	Yellowish liquid
Boiling Point:	>165°C (approx). Decomposition occurs over the range 60 - 305°C.
Freezing Point:	6°C (pour point)
Specific gravity:	0.98 at 20°C
Vapour Pressure:	≤ 7 x 10^{-6} kPa at 25°C
Water Solubility:	<1 mg/L at 20°C
Partition Co-efficient (n-octanol/water):	log P_{ow} = 0.86 to > 6.2 at 20.5°C
Hydrolysis as a Function of pH:	Not conducted due to low water solubility.
Adsorption/Desorption:	Log K_{ow} = 1.45 – 4.24

Dissociation Constant:	Not conducted due to low water solubility.
Flash Point:	146°C (Closed cup)
Particle Size:	Not applicable. Chemical is a liquid.
Flammability Limits:	Not flammable
Autoignition Temperature:	368°C
Explosive Properties:	Not explosive
Reactivity/Stability:	Expected to be stable under normal environmental conditions.

3.1 Comments on Physico-Chemical Properties

Physico-chemical properties were determined by Huntingdon Life Sciences Ltd (1999a). The melting point was determined using the pour point method of OECD TG 102 and the boiling point by the ebulliometric method of OECD TG 103. Boiling was observed from 260ºC with decomposition occurring between 60-305ºC

Relative density was measured using the pycnometer method of OECD TG 109.

Vapour pressure was determined by vapour pressure balance method according to OECD TG 104. The pressure decreased with progressive runs, possibly due to the more volatile components being lost during each run.

The water solubility of the notified substance was tested using a modified OECD TG 105 method based on the light scattering effect of a suspension. However, the substance when added at 1 mg/L was found to form an intractable suspension immediately upon contact with water and could not be solubilised at any concentration. Two unsuccessful attempts were made using the column elution method. Therefore the water solubility was concluded to be <1 mg/L.

Hydrolysis tests were not performed due to the low water solubility of the notified chemical. The structure of the chemical contains functionality which is amenable to hydrolysis but the low water solubility should prevent this from occurring in the environmental pH range 4-9.

The partition coefficient was initially estimated using the Syracuse Log Pow computer model and the calculated log P ranged from 1.77 to 6.97. The partition coefficient was then determined by the HPLC method of OECD TG 117 but the surfactant nature of the substance indicates the results should be treated with caution.

Adsorption/desorption was initially estimated using the Syracuse computer model and the log K_{ow} ranged from 1.45 to 4.24. The partition coefficient was then determined by HPLC as described in OECD draft document TGP 94.75 (April 1994) and again the surfactant nature of the substance indicates the results should be treated with caution. The result range indicated that the notified chemical is likely to have a very high to slight mobility in soils.

The dissociation constant was not determined due to the low water solubility of the chemical.

Surface tension was determined by surface tension/tension balance using the OECD 115 harmonised ring method. The surface tension of a 0.5 g/L solution of the notified chemical was 29.53 mN/m and of a 1 mg/L solution was 51.06 mN/m comfirming the surface active nature of the notified chemical.

4. PURITY OF THE CHEMICAL

Degree of Purity: > 50%

Additives/Adjuvants: None

5. USE, VOLUME AND FORMULATION

Promidium CO will be used as a foam booster or fragrance solubiliser in industrial detergent formulations at up to 5% and personal care products such as shampoos at up to 4%. The notified chemical will be imported in neat liquid form in 200L high density polyethylene drums and also in finished shampoos in 125, 200 and 500mL plastic bottles at up to 4%.

Formulated industrial detergent products containing up to 5% notified chemical will be packaged into containers ranging in size from 0.5 L to 200L.

Less than 20 tonnes of Promidium CO will be imported annually for the first 5 years.

6. OCCUPATIONAL EXPOSURE

Import and Transport

A total of 4 forklift operators, 2 custom clearing agents and one truck driver will handle imported polyethylene drums of neat liquid notified chemical or plastic bottles of finished personal care product containing up to 4% notified chemical. These drums and bottles will not be opened either prior to blending into industrial detergent formulations or end-use respectively. Therefore, these workers will be exposed to the notified chemical only following accidental puncture of import containers.

Retail store personnel will also stack bottles of personal care product for sale. Similarly, these workers may be exposed to the notified chemical but only in the advent of accidental puncture of the product containers.

A single truck driver and 3 drum disposal workers will handle used polyethylene drums. For these workers, dermal and to a lesser extent ocular exposure may occur from contact with drums contaminated with spilt chemical.

Blending of Industrial Detergent Formulations

The notifier claims few details are available regarding handling during formulation although

an average worker exposure duration of 1-2 hours/day, 200 days/year for a single formulation worker has been provided. In the absence of detailed information, it is likely that drums of notified chemical will be opened manually by the single worker and the contents transferred to a mixing vessel via a spear connected to a pump or in some cases, pouring from import containers. In both cases, dermal and ocular exposure to the notified chemical is possible from slops, spills and drips.

In the mixing vessel, the notified chemical will be blended with additional components and transferred to filling machines where the formulation will be decanted into 0.5 – 200 L containers. It is likely that a high level of automation and enclosed transfer lines will largely prevent worker exposure during reformulation. In addition, reformulation will dilute the notified chemical to less than 5% and so any exposure to the notified chemical in the final product will be limited.

Although the vapour pressure of the notified chemical is low, it is possible that agitation associated with the mixing and filling processes will produce aerosols. If local exhaust ventilation is not fitted to mixers and filling machines, inhalation exposure to the notified chemical may occur.

One or two maintenance workers will be exposed to the notified chemical as residues on plant equipment. Potential exposure for up to 1 hour/day, 10 days/year is expected to be mainly dermal.

Although no details were provided regarding personal protective equipment to be worn by formulation and maintenance workers, it is likely that workers will wear impervious coveralls and gloves to limit exposure to the notified chemical as well as other formulation components.

End-use – Cleaning

Containers of industrial detergent formulations containing up to 5% notified chemical will be opened manually and the contents diluted approximately 20-fold with water. Dermal and ocular exposure is likely from slops and splashes during the diluting of notified chemical and from “mop and bucket” applications. It is likely that in addition to coveralls, plastic or rubber gloves may be used to limit dermal exposure during these activities. However, the extent of use may vary considerably.

7. PUBLIC EXPOSURE

Public exposure to the notified chemical through importation and transportation is negligible. Public exposure through processing is likely to be negligible. Public exposure through waste disposal is negligible.

Promidium CO will be used as a foam booster or fragrance solubiliser in industrial detergent formulations at concentrations up to 5%, and personal care products such as shampoos at up to 4%. Public exposure is significant.

8. ENVIRONMENTAL EXPOSURE

8.1 Release

The notifier estimates that < 10 kg/annum of the notified chemical may remain in the import drums after 'emptying'. Residues will be released via the drum recycling process or into landfill.

Rinse water from the cleaning of the blending equipment would release the notified chemical to the waste water system. The notifier has not accounted for the expected volume from this release route but it can be estimated that up to 100 kg per annum of the import volume may be released in this way. The notifier has also discussed the potential release to landfill due to accidental spillages but has not accounted for the volume expected. It can be estimated that up to a further 50 kg per annum may be released to the environment in this way.

The notifier also estimates that up to 200 kg per annum of the notified chemical may be lost as residues remaining in the end use cleaning and personal care containers. This waste would be expected to be disposed to landfill along with the containers.

The major release of the notified chemical will be through use as personal care products and industrial cleaners. It is anticipated that these uses will result in almost all the remaining imported chemical being discharged to sewers throughout Australia.

It is to be expected that the personal care products (eg shampoos) containing the notified chemical may be used by an individual as often as every 1-2 days. The majority of release of the notified chemical is expected to occur at this time. Very little of the chemical is expected to remain in the hair after washing and virtually all of the product containing the notified chemical will be washed off the hair into the sewer. Released product is expected to be treated with the sewage before being released to the environment. The industrial cleaning products containing the chemical are expected to be released to the sewer during and after use. The cleaning products will be used in "mop and bucket" applications. Consequently, a Predicted Environmental Concentration (PEC) estimate has been calculated assuming all of the notified chemical will ultimately be released to the aquatic environment (see Environmental Hazard section).

8.2 Fate

Biodegradability of the notified chemical was determined using the CO_2 Evolution Test (OECD TG 301B, Directive 92/69/EEC) (Huntingdon Life Sciences Ltd, 1999b). The test substance was biodegraded by 10% after approximately 2 days incubation, 46% after 14 days and 61% by the end of the test on day 29. The notified chemical cannot be considered to be readily biodegradable as it did not reach 60% degradation within ten days of the level achieving 10%. The control (10 mgC/L sodium benzoate) achieved 67% degradation after 6 days and 85% after 29 days in the absence of Promidium CO and 66% after 5 days in another reference solution that contained both sodium benzoate and Promidium CO at 10 mgC/L each.

The notified chemical in personal care products and industrial cleaners would be expected to be released to the environment via consumer use through rinsing the chemical off the hair/body or disposing the wash water from industrial cleaning into the sewerage system. In

the sewer, it is anticipated that most will adsorb to sewage sludge due to the surface activity and low water solubility of the chemical. The sludge will either be landfilled or incinerated. Incineration products will include water and oxides of carbon and nitrogen.

The low molecular weight, log Pow (0.86 to >6.2) and low water solubility (< 1 mg/L) of the notified chemical indicate that the notified chemical has the potential to bioaccumulate (Connell, 1990). However, bioaccumulation may be moderated by the inherent biodegradability and expected adsorption to the organic components of sediments and soils.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Summary of the acute toxicity of Promidium CO.

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} > 2000mg/kg	Mason (1999a)
acute dermal toxicity	rat	LD_{50} > 2000mg/kg	Mason (1999b)
skin irritation	rabbit	persistently irritating	Mason (1999c)
skin irritation (5% solution)	human	not irritating	Eisenberg (1997)
eye irritation	rabbit	moderately irritating	Mason (1999d)
skin sensitisation	guinea pig	not sensitising	Coleman (1999)

9.1.1 Oral Toxicity (Mason, 1999a)

Species/strain:	Rat, Sprague Dawley
Number/sex of animals:	3 males, 3 females
Observation period:	14 days
Method of administration:	Gavage
Test method:	OECD TG 401
Mortality:	None
Clinical observations:	No mortalities occurred and all animals gained weight throughout the study. Piloerection, hunched posture and abnormal faeces and ungroomed appearance were observed in all rats. Increased salivation was observed in two males and one female and waddling/unsteady gait was observed in one male and all females. One female was observed walking on toes and one

	female showed increased sensitivity to touch. Recovery as judged by external appearance and behaviour was complete in all animals by day 5.
Morphological findings:	No abnormalities were observed during macroscopic examinations.
LD_{50}:	> 2000mg/kg
Result:	The notified chemical was of very low acute oral toxicity in rats.

9.1.2 Dermal Toxicity (Mason, 1999b)

Species/strain:	Rat, Sprague Dawley
Number/sex of animals:	5 males, 5 females
Observation period:	14 days
Method of administration:	24 hour application to shaved skin via 50 x 50 cm porous gauze pad covered with waterproof dressing.
Test method:	OECD TG 402
Mortality:	None
Clinical observations:	No mortalities occurred and all animals gained weight throughout the study. Vocalisation and hyperactivity were observed in one female on day 1. Slight to well-defined dermal irritation resolving by day 9 was seen in four males and three females. Additional desquamation was observed in two females with localised spots and/or scabbing in one female. These were resolved by day 13.
Morphological findings:	No abnormalities were observed during macroscopic examinations.

Draize scores:

	Time after treatment (days)												
Animal #	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***15***
Erythema													
1	1 [i]	0	0	0	0	0	0	0	0	0	0	0	0
2	1	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0
4	1	1	0	0	0	0	0	0	0	0	0	0	0
5	2	1	0	0	0	0	0	0	0	0	0	0	0
6	1	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0
8	1	1[a]	2[a]	2[a]	1[a]	1[a]	0	0	0	0	0	0	0
9	1[b]	2[b]	2[a]	2[a]	2[a]	2[a]	2[a]	1[b]	0[b]	0[b]	0[b]	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0
Oedema													
1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0
4	1	0	0	0	0	0	0	0	0	0	0	0	0
5	1	0	0	0	0	0	0	0	0	0	0	0	0
6	1	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	1	2	1	1	0	0	0	0	0	0	0	0
9	1	1	1	2	2	2	1	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0

[i] See Attachment 1 for Draize scales
[a] Desquamation (characterised by dryness and sloughing of the skin)
[b] Spots and/or scabbing (localised response)

LD_{50}: > 2000 mg/kg

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

9.1.3 Inhalation Toxicity

Data were not provided.

9.1.4 Skin Irritation (Mason, 1999c)

Species/strain: Rabbit, New Zealand white

Number/sex of animals: 3 males

Observation period: 14 days

Method of administration: 4 hour application of 490mg (0.5mL) test substance to shaved skin via a 2.5 x 2.5 cm porous gauze pad covered with elastic adhesive dressing. One animal was treated additionally with a 3 minute and 1 hour exposure to the test substance.

Test method: OECD TG 404

Draize scores:

		Time after treatment (days)												
Animal #	***60 min***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***
Erythema														
1[a]	0[d]	0	0	0	0	-	-	-	-	-	-	-	-	-
1[b]	0	0	0	0	0	-	-	-	-	-	-	-	-	-
1[c]	2	1	1	1[e]	2[e]	2[e]	2[e]	2[e]	1[e]	1[f]	1[f]	1[f]	1[f]	1[f]
2[c]	1	1	1[e]	2[e]	2	2	1	1[f]	1[f]	1[f]	1[f]	1[f]	1[f]	1[f]
3[c]	2	2	2[e]	2[e]	2[e]	1[e]	1[f]	1[f]	1[f]	1[f]	1[f]	0[f]	-	-
Oedema														
1[a]	0	0	0	0	0	-	-	-	-	-	-	-	-	-
1[b]	0	0	0	0	0	-	-	-	-	-	-	-	-	-
1[c]	1	0	0	0	0	0	0	0	0	0	0	0	0	0
2[c]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3[c]	0	0	0	0	0	0	0	0	0	0	0	0	-	-

[a] Exposure time 3 minutes [b] Exposure time 1 hour [c] Exposure time 4 hours
[d] See Attachment 1 for Draize scales
[e] Thickening
[f] Desquamation (characterised by dryness and sloughing)

Comment: All animals gained weight and none displayed signs of toxicity or ill health during the study.

No irritation was observed in a single animal following 3 or 60 minute exposure. Following 4 hour exposure, thickening of the skin, desquamation and well-defined erythema with or without slight oedema were noted. Very slight erythema was still evident in two out of three animals at day 14.

Result:	The notified chemical was persistently irritating to the skin of rabbits.

9.1.5 Skin Irritation - Human Patch Test (Eisenberg, 1997)

Number/sex of subjects	5 males, 48 females
Observation period:	14 days
Method of administration:	48 hour exposure of 0.2ml of 5% test substance in water applied to interscapular skin via 4.5 cm^2 gauze portion of an occlusive adhesive dressing. Irritation was assessed at patch removal and 24 hours later. A similar reapplication of 5% test substance in water under both occlusive and semi-occlusive conditions was conducted in subjects showing positive responses.
Clinical Observations:	Three subjects discontinued participation in the study for reasons unrelated to the test substance. Two female subjects exhibited a mild and moderate response respectively at 72 hours post application. An additional evaluation, conducted 48 hours post patch removal, showed mild responses in both subjects. Reapplication of test substance showed a positive response in one subject under occlusive conditions. However, in the same subject, semi-occlusive application was negative and so the positive response was considered clinically insignificant. Also, the lack of a reproducible response in the other originally positive subject suggested that the initial positive response was idiosyncratic in origin and clinically insignificant.
Result:	A 5% solution of notified chemical was not irritating to the skin of humans.

9.1.6 Eye Irritation (Mason, 1999d)

Species/strain:	Rabbit, New Zealand white
Number/sex of animals:	3 males
Observation period:	14 days
Method of administration:	0.1 mL test substance instilled into the lower everted lid of one eye; contralateral eye remained untreated.

Test method: OECD TG 405

Draize scores of unirrigated eyes:

	Time after instillation													
Animal #	***1 hour***		***3 hours***		***1 day***		***2 days***		***3 days***		***4 days***		***7 days***	
Cornea	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***	***o***	***a***
1	0[1]	0	-	-	1	1	1	4	1	4	1	4	0	0
2	0	0	D	4	2	1	2	1	0	0	0	0	0	0
3	0	0	D	4	1	4	2	2	1	1	1	1	0	0
Iris														
1	0		0		0		0		1		1		0	
2	0		0		0		0		0		0		0	
3	0		0		0		0		0		0		0	
Conjunctiva	***r***	***c***	***r***	***c***	***r***	***c***	***r***	***c***	***r***	***c***	***r***	***c***	***r***	***c***
1	3	3	-	-	3	3	3	2	3	2	3	2	1	1
2	2	2	3	4	2	2	2	2	2	1	1	0	0	0
3	3	3	3	4	3	2	3	2	3	2	2	1		0

[1] see Attachment 1 for Draize scales
o = opacity a = area r = redness c = chemosis
D = Dulling of the cornea

Comment: Corneal opacification was observed in all animals 24 hours after instillation of the test substance. In addition, diffuse red colouration of conjunctivae with eyelid swelling was also observed up to day 7. Iridal inflammation was observed up to day 14 in one animal.

No animal displayed signs of toxicity or ill health during the study.

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

9.1.7 Skin Sensitisation (Coleman, 1999)

Species/strain: Guinea pig, Dunkin/Hartley albino

Number of animals: Control group: 5 females
Test group: 10 females

Induction procedure: Intradermal injections followed by dermal application

test group:

day 0 — Three pairs of 0.1mL intradermal injections into the shaved neck region:

- Freunds complete adjuvant (FCA)/water 1:1
- Test substance 0.5% in water
- Test substance 0.5% in FCA/saline 1:1

day 7

- 0.4 mL of 50% test substance in water applied via filterpaper patch to shaved neck region and held under occlusive dressing for 48 hours.

control group: Treated similarly to test animals omitting test substance from intradermal injections and topical applications

Challenge procedure:

day 21 — 0.2 mL of 5% and 10% test substance in water applied via filterpaper patch to shaved neck region and held under occlusive dressing for 24 hours.

Test method: OECD TG 406, Magnusson and Kligman maximisation test

Challenge outcome:

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

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

Comment: In both test and control animals, necrosis was observed at sites of injection of FCA. Slight irritation was observed in test and control animals at sites of injection of test substance in water and sterile water respectively.

No dermal reactions were observed in any control or test animal during topical induction or challenge.

All animals gained weight during the study.

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

9.2 7-Day Repeated Dose Toxicity (Jones, 1999a)

Species/strain: Rat, Charles River albino

Number/sex of animals: 3 males and 3 females per dose

Method of administration: Gavage

Dose/Study duration: 0, 100, 500, 1000 mg/kg/day for 7 days.

Test method: OECD TG 407

Clinical observations:
Transient post-dosing salivation (sometimes brown in colour) was observed occasionally for all animals receiving 1000 mg/kg/day and for 2 animals of each sex receiving 500 mg/kg/day.

All animals gained weight during the study. Overall body weight gain for male rats receiving 1000 mg/kg/day was slightly decreased compared to controls. Males receiving 500 mg/kg/day showed a higher overall gain compared to both controls and males given the higher dose. Therefore, changes in weight gain were considered not treatment-related.

No deaths occurred during the treatment period.

Clinical chemistry/Haematology
Clinical chemistry or haematological tests were not conducted.

Organ Weights and Histopathology:
Organ weights for kidney, liver and spleen in treatment animals were comparable to those of controls. Tissue macroscopic examinations at terminal sacrifice revealed no abnormalities in any animal. No histopathologic studies were conducted.

Result:
No clear evidence of toxicity was observed at any dose. Transient salivation following administration of higher doses was considered unremarkable and consistent with gavage dosing. 1000 mg/kg/day was considered a suitable dose for a 28-day toxicity study.

9.3 28-Day Repeated Dose Toxicity (Jones, 1999b)

Species/strain: Rat, Charles River albino

Number/sex of animals: 5 males and 5 females per dose

Method of administration: Gavage

Dose/Study duration: 0, 15, 150, 1000 mg/kg/day for 28 days

Test method: OECD TG 407

Clinical observations:
Transient post-dosing salivation was observed occasionally for all animals receiving 1000 mg/kg/day and for 4 males receiving 150 mg/kg/day and 2 females receiving 15 mg/kg/day.

All animals gained weight during the study. Body weight gain for all animals receiving 1000mg/kg/day and females receiving 150 mg/kg/day was slightly lower over the first 4 days of treatment compared to controls. A slight non dose-related decrease in weight gain compared to controls was observed in females receiving 1000 and 150 mg/kg/day. In males, however, receiving the highest dose, weight gain was comparable to that of controls.

No deaths occurred during the treatment period.

Clinical chemistry/Haematology
No treatment-related changes in blood chemical or haematological parameters were observed compared to controls. Urine specific gravity was increased significantly in animals of both sexes receiving 1000 mg/kg/day. Urine volume decreased and urine pH increased in high dose males. Urine phosphorus also decreased in high dose males. Urine potassium decreased in high dose animals of both sexes and females receiving 150 mg/kg/day. Changes in urinary parameters were not reflected by any pathological changes.

Organ Weights and Histopathology:
Absolute and relative thymic weights for females receiving 1000 and 150 mg/kg/day were reduced slightly compared to controls. These were non dose-related in degree and without parallel pathological changes (see below). All other organ weights were similar for treatment groups compared to controls.

No histopathological changes were observed in the thymus to account for decreased thymic weights. In kidneys of male rats receiving 1000 mg/kg/day, focal basophilic cortical tubules were present in 3 out of 5 rats and in 2 rats this was associated with interstitial inflammation. The confine of lesions to a single focus in each animal suggested that changes were unlikely to be treatment-related. In addition, no histopathologic changes were observed to account for increased urinary pH in high dose males.

Comment:
The study authors considered the thymus weight observations not of toxicological significance on the basis of a lack of a dose relationship and histopathological changes.

Result:
Treatment-related effects consisting of urine volume decreases and pH increases were observed for both sexes at 1000 mg/kg/day. Males receiving this high dose as well as females receiving 150 mg/kg/day showed low urine potassium compared to controls. On this basis, a no observed effect level (NOEL) of 15 mg/kg/day and a no observed adverse effect level (NOAEL) of 1000 mg/kg/day were assigned.

9.4 Genotoxicity

9.4.1 *Salmonella typhimurium* Reverse Mutation Assay (Kitching, 1999)

Strains:	*Salmonella typhimurium* TA98, 100, 1535, 1537; *Escherischia coli* CM891
Metabolic activation:	Aroclor 1254-induced rat liver microsomal fraction S9
Concentration range:	1.5, 5, 15, 50, 150, 500, 1500, 5000 μg/plate
Test method:	OECD TG 471
Comment:	Over two independent mutation tests, toxicity was observed for TA100 at 500 and 1500 μg/plate and all strains at 5000 μg/plate. No significant increases in revertant colony numbers were observed in any strains in the presence or absence of metabolic activation.
Result:	The notified chemical was non mutagenic under the conditions of the test.

9.4.2 Chromosomal Aberration Assay in Human Lymphocytes (Akhurst, 1999)

Cells:	Human lymphocytes
Metabolic activation system:	Aroclor 1254-induced rat liver microsomal fraction S9

Dosing schedule:

Metabolic Activation	***Study Number***	***Test concentration (μg/mL)***	***Controls***
-S9	Initial study	Treatment time = 3 hours; recovery time = 18 hours 62.5, 125 and 250 μg/mL	Positive: Mitomycin C Negative: Water vehicle
	Confirmation study	Treatment time = 21 hours 62.5*, 100 and 125* μg/mL	
+S9	Initial study	Treatment time = 3 hours; recovery time = 18 hours 125, 250 and 300 μg/mL	Positive: Cyclophosphamide

	Confirmation study	Treatment time = 3 hours; recovery time = 18 hours. 300*, 400 and 500 μg/mL	Negative: Water vehicle
	Second confirmation study	Treatment time = 3 hours; recovery time = 18 hours. 450 and 500 μg/mL	

* - cultures selected for metaphase analysis

Test method: OECD TG 473

Comment: Precipitation was observed in culture medium in both the presence and absence of metabolic activation at concentrations of 250 μg/mL and above.

In the initial study, both in the presence or absence of metabolic activation, the test substance produced no statistically significant increase in the proportion of metaphase figures containing chromosomal aberrations at any dose level. This negative result was also observed in the confirmation test in the absence of metabolic activation. However, with metabolic activation in two confirmation tests, the test substance induced a statistically significant increase in the proportion of metaphase figures containing chromosomal aberrations at 450 and 500 μg/ml.

These non-reproducible increases in frequencies of chromosomal aberrations were observed only at cytotoxic levels of test substance (causing approximately 50% reduction in mitotic index). Effects may be related to surfactant activity rather than a genotoxic mechanism.

Result: The notified chemical was not likely to be clastogenic under the conditions of the test.

9.4.3 Micronucleus Assay in the Bone Marrow Cells of the Mouse (Mason, 1999)

Species/strain: Mouse, CD-1 outbred albino

Number and sex of animals: 5 males per dose plus an additional 5 males for 0 and 1000 mg/kg doses

Doses: 0, 250, 500 and 1000 mg/kg

Method of administration: Intraperitoneal injection using water as vehicle; an additional positive control group received test substance in water by gavage.

Test method:	OECD TG 474
Comment:	A preliminary toxicity test for doses up to 2000 mg/kg was conducted using 2 males and 2 females per dose. Severe clinical signs were observed in both sexes with 1500 and 2000 mg/kg. For tested doses up to 1000 mg/kg, no statistically significant increases in the frequency of micronucleated immature erythrocytes at 24 and 48 hours after treatment were observed compared to controls. A decrease in the frequency of micronucleated immature erythrocytes at 1000 mg/kg was ascribed to the surfactant nature of the test substance.
Result:	The notified chemical was non clastogenic under the conditions of the test.

9.4.4 Rat Liver DNA Repair (UDS) Test (Mehmood, 2000)

Species/strain:	Rats, Hsd/Ola Sprague-Dawley
Number and sex of animals:	5 males per dose per exposure period
Doses:	0, 600 and 2000 mg/kg
Method of administration:	Oral (gavage) using water as vehicle
Test method:	OECD TG 486
Comment:	A preliminary toxicity test showed that a maximum dose of 2000 mg/kg was not accompanied by clinical signs other than mild piloerection. No statistically significant increases in hepatocyte total or net nuclear grain counts were observed for either 2 or 14 hour exposure to the test substance.
Result:	The notified chemical did not induce DNA damage under the conditions of the test.

9.5 Overall Assessment of Toxicological Data

In acute toxicity tests, the notified chemical was shown to possess very low oral and low dermal toxicity with a rat LD_{50} for both tests established at >2000 mg/kg. Inhalation toxicity data were not provided.

A skin irritation test in rabbits showed that 4 hour exposure to the notified chemical induced

thickening of the skin, desquamation and well-defined erythema in the presence or absence of slight oedema. Slight erythema was evident at day 14. In a human patch test of a 5% aqueous solution, although mild or moderate responses were observed in 2 of 50 subjects they were not reproducible following reapplication and so were regarded as idiosyncratic in origin and not of clinical significance.

An eye irritation test revealed corneal opacification in all animals 24 hours after instillation of the notified chemical. In addition, diffuse red colouration of conjunctivae with eyelid swelling were also observed up to day 7. In one animal, iridal inflammation was evident up to day 14.

A skin sensitisation study in guinea pigs revealed that the notified chemical was not dermally sensitising.

No clear clinical or macroscopical evidence of toxicity was observed in a pilot 7-day repeated dose oral toxicity test in rats. In a more intensive 28-day study, a no observed effect level (NOEL) of 15 mg/kg/day and a no observed adverse effect level (NOAEL) of 1000 mg/kg/day were assigned.

The notified chemical was shown to be non mutagenic in an *in vitro* bacterial mutation assay. In an i*n vivo* chromosome aberration assay, increases in frequencies of chromosomal aberrations were observed but only at cytotoxic levels of test substance and the increases were non-reproducible. On this basis, the notified chemical may be regarded as non clastogenic. A mouse micronucleus assay showed no significant increases in the induction of micronucleated immature erythrocytes indicating non clastogenicity also in this assay. Similarly, a DNA repair test showed no significant increases in nuclear grain counts in hepatocytes indicating that the notified chemical failed to induce DNA damage.

On the basis of these toxicological data, the notified chemical should be determined hazardous and classified Irritant (Xi) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999). The notified chemical should carry the risk phrases R36/38 – Irritating to Eyes and Skin.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

Test	*Species*	*Results*
Acute toxicity [OECD 203]	rainbow trout *Oncorhynchus mykiss*	LC50 (96 h) = 5.2 mg/L NOEC = 0.8 mg/L
Acute toxicity [OECD 202]	*Daphnia magna*	EC50 (48 h) = 2.2 mg/L NOEC = 1.1 mg/L
Growth inhibition [OECD 201]	Algae *Selenastrum capricornutum*	EbC50 (72 h) = 0.72 mg/L ErC50 (72 h) = 3.3 mg/L NOEC = 0.20 mg/L

Respiration inhibition [OECD 209]	Activated sludge	EC50 (3 h) = >100 mg/L

* NOEC - no observable effect concentration

Fish (Huntingdon Life Sciences Ltd, 1999c)

Rainbow trout were exposed to five solutions of the notified substance at nominal concentrations of 1.0, 2.2, 4.6, 10 and 22 mg/L for a period of 96 hours under semi-static test conditions. One aquarium at each concentration plus a dilution water control were set up with seven fish per tank. Each solution was sampled and analysed for notified chemical concentration at the start of the test and at 24 h, 72 h and 96 h. The mean measured exposure concentration for the above nominal solutions were 0.81, 1.8, 3.4, 8.0 and 19 mg/L. These are all well above the water solubility limit of the notified chemical though there is no mention of the state of the solutions in the report. No co-solvent appears to have been used in the preparation of the solutions.

After 24 h exposure, 100% mortality occurred at 22 mg/L (nominal). At 72 h, 100% mortality was observed at 10 mg/L. No mortality was observed in the other concentrations. However, all of the surviving fish at 4.6 mg/L and some of the fish at 2.2 mg/L exhibited sublethal effects such as increased pigmentation, long faecal trail, hyperventilation, swimming on the surface and lying on the bottom. The LC50 values were calculated using the Thompson and Weil model (Thompson & Weil, 1952).

Aquatic Invertebrates (Huntingdon Life Sciences Ltd, 1999d)

Daphnia were exposed to five solutions of the notified substance at nominal concentrations of 0.46, 1.0, 2.2, 4.6 and 10 mg/L without co-solvent for a period of 48 hours under static test conditions. Twenty daphnia were exposed to Promidium CO in individual vessels at each concentration plus a dilution water control. Each solution was sampled and analysed for Promidium CO concentration at the start of the test and at 48 h. The geometric mean measured exposure concentration for the above nominal solutions were 0.066, 0.099, 1.1, 3.7 and 10 mg/L. The large losses at the lower concentrations were believed to be biological.

100% immobilisation occurred at 10 mg/L (nominal) after 24 h. After 48 h exposure 80% immobilisation occurred at 4.6 mg/L with 40% immobilisation having occurred at 24 h. No immobilisation was observed at other concentrations. The EC50 (48 h) = 2.2 mg/L was calculated using the Thompson and Weil model (Thompson & Weil, 1952).

Algae (Huntingdon Life Sciences Ltd, 1999e)

1 x 10^5 cells/mL of the green algae Selenastrum capricornutum in triplicate were exposed to six solutions of the notified substance at nominal concentrations of 0.22, 0.46, 1.0, 2.2, 4.6 and 10 mg/L for a period of 72 hours under closed system test conditions. An untreated control with six replicates was also set up and kept under the same conditions as the test solutions. Each solution was sampled and analysed for Promidium CO concentration at the start of the test and at 72 h. The geometric mean measured exposure concentration for the above nominal solutions were 0.045, 0.066, 0.096, 0.14, 0.20 and 0.31 mg/L.

After 72 hours exposure of the notified chemical to green algae *Selenastrum capricornutum*, the EbC50 was determined to be 0.085 mg/L, the ErC50 was 0.18 mg/L and the no observed effect concentration was determined to be 0.045 mg/L using the geometric mean measured

concentrations. However, the initial measured concentration are believed to be more biologically relevant as these are the concentrations that produced the observed inhibitory effects before degradation of the chemical occurred. Adsorption to the algal mass is likely to have been significant. Using the initial measured concentrations the EbC50 (72 h) was 0.72 mg/L, the ErC50 was 3.3 and the NOEC was 0.20 mg/L.

Sludge (Huntingdon Life Sciences Ltd, 1999f)

A test on the inhibition of the respiration of activated sludge was also conducted. The test substance was suspended in dechlorinated water at nominal loadings of 1, 10 and 100 mg/L. The test flasks were prepared by preparing the suspensions of Promidium CO at the various concentrations (1 sample each at the two lower concentrations and 3 replicates at the highest concentration) adding synthetic sewage and then the microbial inoculum (suspended solids 1.6 g/L). Following a 3 hour aeration the contents of the flasks were poured into darkened 300 mL BOD bottles fitted with oxygen sensing electrodes. The rate of oxygen consumption was measured for the dispersions, and compared with that in a control vessels. None of the tests indicated any significant inhibition of bacterial respiration compared with the controls, and it was concluded that the new chemical is not toxic to sewage bacteria.

A reference test conducted with 3,5-dichlorophenol the EC50 was calculated to be 9.7 mg/L, meeting the criteria for a valid test.

Conclusion

The ecotoxicity test results submitted for the notified substance suggests that it is not toxic to bacteria, is moderately toxic to fish and aquatic invertebrates but highly to very highly toxic to algae.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The vast majority of notified chemical will be discharged to sewer through product use. As the product will be used throughout the country, and sent to sewage treatment plants in both city and country locations, a worst case PEC based on continental use has been calculated based on the maximum projected level of use with no removal of the notified chemical during sewerage treatment:

Maximum import volume per annum	20 tonnes
Amount discharged to sewer	98%
Volume discharged per day	53.7kg
Sewer output per day*	2 700 ML
Concentration in Sewage Treatment Plant	19.6 µg/L
Concentration in sewage after 0% (estimated) adsorption to sewage sludge	19.6 µg/L
Further diluted (1:10) in receiving waters	1.96 µg/L

*Sewer output based on an Australian population of 18 million, each using 150 L water per day.

The Safety Factor for this chemical, based on algae, having the lowest LC50 (720 µg/L) and the PEC worst case scenario is approximately 370. However, this assumes maximum import volumes and that the notified chemical would adsorb to sewage sludge (indicated by the low

solubility and surfactant properties). A PEC based on continental use has also been calculated, based on the maximum projected level of use with 50% removal of the notified chemical during sewerage treatment:

Maximum import volume per annum	20 tonnes
Amount discharged to sewer	98%
Volume discharged per day	53.7 kg
Sewer output per day*	2 700 ML
Concentration in Sewage Treatment Plant	19.6 μg/L
Concentration in sewage after 50% (estimated) adsorption to sewage sludge	9.8 μg/L
Further diluted (1:10) in receiving waters	0.98 μg/L

*Sewer output based on an Australian population of 18 million, each using 150 L water per day.

The Safety Factor for the chemical, based on algae, having the lowest LC50 (720 μg/L) and the PEC (with 50% removal in the treatment plant) is approximately 730 and suggests the notified chemical should not pose a potential environmental hazard. The PEC is estimated conservatively and the inherently biodegradable nature of the notified chemical is likely to diminish the risk associated with its use up to the maximum levels proposed.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Hazard Assessment

In acute toxicity tests, the notified chemical was shown to possess very low oral and low dermal toxicity. Inhalation toxicity data were not provided.

A skin irritation test in rabbits showed thickening of the skin, desquamation and well-defined erythema in the presence or absence of slight oedema. Slight erythema was still evident at day 14. In a human patch test of a 5% aqueous solution, positive responses were observed in a minority of subjects but these appeared idiosyncratic in origin and not of clinical significance. An eye irritation test revealed corneal opacification in all animals. In addition, diffuse red colouration of conjunctivae with eyelid swelling were also observed. In one animal, iridal inflammation was evident up to day 14.

A skin sensitisation study in guinea pigs revealed that the notified chemical was not dermally sensitising.

No clear clinical or macroscopical evidence of toxicity was observed in a pilot 7-day repeated dose oral toxicity test in rats. In a more intensive 28-day study, a no observed effect level (NOEL) of 15 mg/kg/day and a no observed adverse effect level (NOAEL) of 1000 mg/kg/day were assigned.

The notified chemical was shown to be non mutagenic in an *in vitro* bacterial mutation assay. In an i*n vivo* chromosome aberration assay, although increases in frequencies of chromosomal aberrations were observed, these were only at cytotoxic levels of test substance and the increases were non-reproducible. A mouse micronucleus assay also failed to indicate clastogenic properties of the notified chemical. Additionally, evidence of DNA damage was

not observed in a DNA repair test in hepatocytes.

On the basis of these toxicological data, the notified chemical is determined hazardous and classified Irritant (Xi) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999) with the risk phrases R36/38 – Irritating to Eyes and Skin.

Occupational Health and Safety

The notified chemical will be imported in neat liquid form in 200L high density polyethylene drums and also in finished shampoos in 125 - 500 mL plastic bottles at up to 4%. Formulated industrial detergent products containing up to 5% notified chemical will be packaged into containers ranging in size from 0.5 L to 200L.

Occupational exposure to the notified chemical is unlikely during import, transport and storage and would only be envisaged following accidental puncture of the polyethylene drums or plastic bottles. If exposure to neat notified chemical occurs, skin and eye irritation would be expected. Irritation of lesser severity may also occur upon prolonged exposure to formulated products containing diluted notified chemical.

The notified chemical will be used to formulate industrial detergent products. Dermal and ocular exposure to the notified chemical may occur from spillage during initial charging of the mixing vessel with the imported liquid chemical. Exposure to diluted notified chemical may occur also from slops and splashes during the filling of product containers. In addition, inhalation exposure is possible from fugitive aerosols generated from the mixing process. Maintenance workers are likely also to experience dermal exposure with the notified chemical during routine plant maintenance. Dermal or ocular contact with the notified chemical especially in neat form would be expected to result in persistent irritation. Respiratory irritation would be expected also if inhalation exposure occurs.

In this respect, personal protective equipment consisting of impervious coveralls gloves and eyewear should be worn when handling the neat notified chemical.

During end-use, cleaning workers may be exposed to the notified chemical mainly via the dermal route during “mop and bucket” applications of industrial cleaning solutions containing up to 5% notified chemical. Although acute exposure is unlikely to result in health effects, prolonged or repeated exposure may result in dermal and/or ocular irritation. In addition to protective clothing, plastic or rubber gloves should be used to limit dermal exposure during these activities.

Public Health

As the chemical is used in personal care products, namely shampoo, public exposure is significant. Public exposure through cleaning products is expected to be possible, but less significant. A 60 kg woman applying 12 g of shampoo, containing 4% concentration of the notified chemical, will be exposed to 0.8 mg/kg/d of the chemical (assuming 10% dermal absorption) which is well below the NOEL of 15 mg/kg/d and very well below the acute toxicity of 2000 mg/kg. The notified chemical is a moderate eye irritant, however, shampoo products are known to be eye irritants. The chemical is a slight skin irritant and is not a skin sensitiser. Therefore the notified chemical is not likely to pose a significant threat to public health.

13. RECOMMENDATIONS

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

Regulatory controls

- The NOHSC Chemicals Standards Sub-committee should consider the following health hazard classification for the notified chemical:

  R36/38 – Irritating to Eyes and Skin

Occupational Health and Safety

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:

  Protective eyewear, chemical resistant industrial clothing and footwear and impermeable gloves should be used during occupational use of the neat notified chemical. Where engineering controls and work practices do not to control exposure to aerosols containing the notified chemical, a negative pressure organic vapour and particle respirator should be used;

  During end-use of industrial cleaning products containing up to 5% notified chemical, in addition to protective clothing, plastic or rubber gloves should be used to limit dermal exposure;

  Guidance in selection of protective eyewear may be obtained from Australian Standard (AS) 1336 (Standards Australia, 1994) and Australian/New Zealand Standard (AS/NZS) 1337 (Standards Australia/Standards New Zealand, 1992); for industrial clothing, guidance may be found in AS 3765.2 (Standards Australia, 1990); for impermeable gloves or mittens, in AS 2161.2 (Standards Australia/ Standards New Zealand, 1998); for occupational footwear, in AS/NZS 2210 (Standards Australia/ Standards New Zealand, 1994a); for respirators, in AS/NZS 1715 (Standards Australia/ Standards New Zealand, 1994b) and AS/NZS 1716 (Standards Australia/ Standards New Zealand, 1994c) or other internationally accepted standards;

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Emergency procedures

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

Secondary notification

The NICNAS Director must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act:
- if more than 10 tonnes/year of the notified chemical is to be introduced, due to the narrow safety margin for algae data on the likely extent of adsorption to sludge and sediment may be requested.

(2) Under Section 64(2) of the Act:
- if any of the circumstances listed in this subsection arise.

The Director will then decide whether secondary notification is required.

14. MATERIAL SAFETY DATA SHEET

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

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.

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Attachment 1

The Draize Scale (Draize, 1959) 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 (Draize *et al*., 1944) 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

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