File No: NA/383

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Menthyl pyrrolidone carboxylate

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

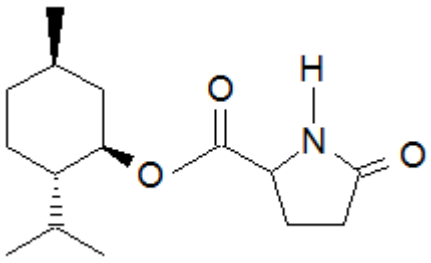
Menthyl pyrrolidone carboxylate

1. APPLICANT

Quest International of 6 Britton St SMITHFIELD NSW 2164 has submitted a limited notification statement with their application for an assessment certificate for menthyl pyrrolidone carboxylate.

2. IDENTITY OF THE CHEMICAL

Chemical name:	D and L proline, 5-oxo-, 5-methyl-2-[1-methylethyl]cyclohexyl ester
Chemical Abstracts Service (CAS) Registry No.:	the notified chemical has no CAS No.; however, the individual D and L isomers have CAS Nos.: D isomer: 68127-22-0; L isomer: 64519-44-4
Other names:	menthyl pyrrolidone carboxylate
Trade name:	QUESTICE
Molecular formula:	$C_{15}H_{25}NO_3$
Structural formula:	



Molecular weight:	267
Method of detection and determination:	gas liquid chromatography

Spectral data:	infrared and nuclear magnetic resonance spectra to confirm structure were provided

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	white/cream soft crystalline solid
Particle Size:	range of particle sizes below 1 mm
Melting Point:	70°C ± 4°C
Specific Gravity:	not determined
Vapour Pressure:	4.23 X 10^{-6} Pa (calculated (1))
Water Solubility:	32 - 4121 mg/L (calculated); 303 mg/L (calculated (1))
Partition Co-efficient (n-octanol/water):	log P_{ow} = 3.0 (calculated); 3.04 (calculated (1))
Hydrolysis as a function of pH:	not determined
Adsorption/Desorption:	log K_{oc} = 2.99 (calculated (1))
Dissociation Constant:	not determined
Flash Point:	not determined
Flammability Limits:	not determined
Autoignition Temperature:	not determined
Explosive Properties:	not determined

Comments on Physico-Chemical Properties

Several of the physical and chemical properties of the notified chemical were not available from the notifier, and have been calculated from the ASTER database (1).

Water solubility was calculated by the notifier using two separate computer models; Chemcalc: Aqueous solubility estimation, which gives a predicted solubility of 32 mg/L; and the Shape-polarising model, giving a predicted solubility of 4121 mg/L. ASTER calculates solubility at 303 mg/L. In environmental terms, this chemical can be considered slightly to moderately soluble.

The notifier has stated the chemical is stable in emulsions, creams or gels between pH 4.5 and 8.5. However, under normal environmental conditions, hydrolysis of this product would be expected. Additionally, in the presence of enzymes such as esterases, the chemical is readily hydrolysed to release menthol. It is this action which gives the chemical its cooling properties when applied to the skin.

Calculated values for partition co-efficient and adsorption/desorption co-efficient are relatively high, indicating the chemical will readily adsorb to soil and sediment.

4. PURITY OF THE CHEMICAL

Degree of purity: > 98%

Toxic or hazardous impurities: none

Non-hazardous impurities (> 1% by weight):

Chemical Name	*CAS No.*	*Weight %*
menthol	89-78-1	< 1%
water	7732-18-5	< 1%

Additives/adjuvants: none

5. USE, VOLUME AND FORMULATION

The notified chemical is a cosmetic ingredient that is used to produce a slow release cooling effect upon the skin. It will be imported as the pure chemical at a rate of up to 800 kg per year for the first five years.

6. OCCUPATIONAL EXPOSURE

The notified chemical will be imported in 10 or 25 kg metal kegs with a double polyethylene liner and shipped to cosmetic manufacturers. Exposure during transport and storage is unlikely except in the event of an accident.

The notified chemical may be used as a component of an aftershave balm, roll-on deodorant, cooling gel or talc at a concentration of up to 3%.

In a typical batch of the cooling gel 0.75 kg of the notified chemical would be manually added to the mixing vessel after weighing out together with fragrance, Ceteareth-20, alcohol and water. Following stirring, the mixture is added to the gel component to a combined weight of 100 kg. The resultant gel is then filled out into 100 g or 200 g plastic tubes or tubs.

In a typical batch of the talcum powder, a powder mixing plant is used to which is added talcum powder, magnesium carbonate, fragrance and preservative as well as 2.0 kg of the notified chemical for each 100 kg batch. Following blending, the product is filled out into suitable plastic or cardboard containers.

7. PUBLIC EXPOSURE

There is negligible potential for public exposure to the notified chemical arising from transport or formulation into cosmetic products.

Persons using cosmetics containing the notified chemical will be exposed to it for prolonged periods, principally via the dermal route. Once applied to the skin, the notified chemical undergoes enzymatic cleavage to form menthol and pyrrolidone carboxylic acid. The most probable fate of the metabolites and any remaining parent chemical is entry into the domestic sewerage system. Small amounts of the notified chemical in discarded cosmetic packages may also be disposed of as garbage.

8. ENVIRONMENTAL EXPOSURE

Release

The chemical will be compounded into cosmetics by cosmetics manufacturing companies. Standard reformulation procedures involve blending or mixing in either open or closed systems. Repackaging is in plastic tubes or tubs or suitable cardboard containers. The sizes of the final product packs are unlikely to exceed 200 g.

Release during reformulation of the notified chemical into various cosmetic products will result from unused residues in containers, equipment washings and batch residues. Maximum losses through these processes are unlikely to be more than 1%, and will be assumed to be released to sewer. This means that, of the maximum import volume of 1000 kg, 10 kg per year will be released to sewer, spread around all reformulation plants. Assuming 200 days per year of reformulation, this is a daily release of 50 g.

The cosmetics are expected to be sold Australia wide providing a wide, but very dispersed environmental exposure of the substance. The major release to the environment is from end use where residues of the notified chemical would be washed or wiped off the face, hands and body and where residues in used “empty” containers would be disposed of with the containers. The notifier has estimated no more than 1 g of end product would remain in containers when entering the waste stream, based on a 200 g container. This equates to 0.5% of the notified chemical released through household garbage to landfill or incineration.

Up to 98.5% of the imported chemical can therefore be expected to be released through end use. While the chemical readily hydrolyses on the skin to release menthol, for a worst case situation, it will be assumed no hydrolysis occurs, and all the notified chemical is released to sewer through washing the end cosmetic from

the body.

Fate

Although the notifier claims the chemical is hydrolytically stable through the range pH = 4.5 to 8.5, hydrolysis could still provide an important breakdown mechanism for this product. When in contact with skin, the presence of certain enzymes causes the chemical to readily hydrolyse, forming menthol and pyrrolidone carboxylic acid.

It is likely that any notified chemical released direct to sewer without hydrolysing on skin will be degraded by the same mechanism within the sewage treatment plant prior to release to receiving waters.

The level 1 Fugacity Model indicates that, at equilibrium, 85.68% of this chemical will partition to water; 14.29% partitioning to soil or sediment; and a negligible proportion partitioning to air or suspended solids. With the relatively high partition co-efficient and adsorption/desorption co-efficient, and only slight to moderate water solubility, a somewhat higher percentage partitioning to soil or sediments than indicated by this model is predicted.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Summary of the acute toxicity of menthyl pyrrolidone carboxylate

Test	*Species*	*Outcome*	*Reference*
acute oral toxicity	rat	LD_{50} = 9.6 g/kg	(2)
acute oral toxicity	mouse	LD_{50} = 4.5 g/kg	(3)
skin sensitisation	guinea pig	non-sensitiser	(4,5,6)

9.1.1 Oral Toxicity (2,3)

9.1.1.1 Oral toxicity in rats (2)

Species/strain:	rat/ Wistar
Number/sex of animals:	3 per sex per dose group (0, 4.0, 6.0, 9.0 and 13.5 g/kg dose groups)
Observation period:	21 days
Method of administration:	gavage in groundnut oil
Clinical observations:	stress, hypothermia, ataxia and coma in the 9.0 and 13.5 g/kg dose groups

Mortality:	no deaths at 0, 4.0 or 6.0 g/kg; 2/6 at 9.0 g/kg and 6/6 at 13.5 g/kg
Morphological findings:	all rats which died revealed irritation of the small intestines and pale livers
Test method:	not specified
LD_{50}:	9.6 g/kg
Result:	the notified chemical exhibited low acute oral toxicity in rats

9.1.1.2 Oral toxicity in mice (3)

Species/strain:	mouse/ unspecified
Number/sex of animals:	3 per sex per dose group (0, 3.00, 4.50, 6.75 and 10.13 g/kg dose groups)
Observation period:	21 days
Method of administration:	gavage in groundnut oil
Clinical observations:	coma, hypothermia, cyanosis and laboured breathing in all mice of the high dose group; in most mice of the 6.75 g/kg dose group with some of the animals exhibiting cyanosis and uncoordinated movement; the mice dosed at 4.50 g/kg were also comatose, hypothermic and showed laboured breathing; most mice of the 3.00 g/kg dose group exhibited hypothermia and one mouse exhibited uncoordinated movement
Mortality:	no deaths in the control; 1/6 in the 3.00 g/kg group; 4/6 in the 4.50 and 6.75 g/kg groups and 6/6 in the 10.13 g/kg group
Morphological findings:	autopsy of the mice which died showed fluid distension of the stomach and small intestine with irritation of the latter; very pale intestines; pale kidneys and pale edges to the liver; the mouse dosed at 3.00 g/kg had pale intestines and kidneys and prominent mesenteric blood vessels
Test method:	not specified

LD_{50}:	4.5 g/kg
Result:	the notified chemical exhibited low acute oral toxicity in mice

9.1.2 Skin Sensitisation (3)

9.1.2.1 Skin Sensitisation (3)

Species/strain:	guinea pig/ Dunkin Hartley
Number of animals:	6 males and 4 females
Induction procedure:	0.1 mL of 0.125% test article in 6% acetone/0.01% dodecylbenzene sulphonate /0.9% saline by injection in the two inguinal and axilliary areas (first induction); 6 days after first challenge (see below) a second induction by the same method was performed
Challenge procedure:	15 days after induction 0.1 mL of 0.05% test article in 6% acetone/0.01% dodecylbenzene sulphonate /0.9% saline by injection in one flank and topical application of 25% test article in acetone of the other flank (first challenge); 14 days after second induction a second challenge using the same procedure was performed; a final confirmatory challenge was carried out in the same manner ten days later with an additional intradermal injection challenge at 0.1% test article; for each challenge sites were examined 24 hours post-treatment
Test method:	not specified
Result:	no positive responses found in any animal at any dose; the notified chemical was not a skin sensitiser in guinea pigs

9.1.2.2 Skin Sensitisation (3)

Species/strain:	guinea pig/ Dunkin Hartley
Number of animals:	6 males and 4 females
Induction procedure:	0.1 mL of 0.188% test article in 6% acetone/0.01% dodecylbenzene sulphonate /0.9% saline by injection in the two inguinal and axilliary areas (first induction); 8 days

	after first challenge (see below) a second induction by the same method was performed
Challenge procedure:	14 days after induction 0.1 mL of 0.075% test article in 6% acetone/0.01% dodecylbenzene sulphonate /0.9% saline by injection in one flank and topical application of 20% test article in acetone of the other flank (first challenge); 14 days after second induction a second challenge using the same procedure was performed; a final confirmatory challenge was carried out in the same manner 7 days later; for each challenge sites were examined 24 hours post-treatment
Test method:	not specified
Result:	no positive responses found in any animal at any dose; the notified chemical was not a skin sensitiser in guinea pigs

9.1.2.3 Skin Sensitisation (3)

Species/strain:	guinea pig/ Dunkin Hartley
Number of animals:	6 males and 4 females
Induction procedure:	0.1 mL of 0.188% test article in 6% acetone/0.01% dodecylbenzene sulphonate /0.9% saline by injection in the two inguinal and axilliary areas (first induction); 9 days after first challenge (see below) a second induction by the same method was performed
Challenge procedure:	13 days after induction 0.1 mL of 0.075% test article in 6% acetone/0.01% dodecylbenzene sulphonate /0.9% saline by injection in one flank and topical application of 20% test article in acetone of the other flank (first challenge); 13 days after second induction a second challenge using the same procedure was performed; a final confirmatory challenge was carried out in the same manner 8 days later; for each challenge sites were examined 24 hours post-treatment
Test method:	not specified
Result:	no positive responses found in any animal at any dose; the notified chemical was not a skin

sensitiser in guinea pigs

9.2 Repeated Dose Toxicity (2,4)

9.2.1 3 week feeding study in rats (2)

Species/strain:	rat/ Wistar
Number/sex of animals:	8 male/ 8 female animals per dose group
Method of administration:	dietary
Dose/Study duration::	0, 0.1%, 0.5%, 1.0% and 2.0%/ 3 weeks
Clinical observations:	significantly reduced body weight gain in the high dose group
Clinical chemistry/Haematology	*clinical chemistry*: effects were seen in the 1.0% and 2.0% dose groups; elevated serum magnesium and creatinine in males and females; elevated lactate dehydrogenase, 1-hydroxybutyrate dehydrogenase and isocitrate dehydrogenase in males; elevated pseudocholinesterase in females; in addition males in the 2.0% dose group showed elevated creatinine kinase; all changes were ascribed to metabolic adjustment associated with reduced food intake *haematology*: normal *urinalysis*: normal
Histopathology:	significantly higher liver weights in males and females in the 2.0% dose group were not correlated with histological changes; other changes, viz., depletion of periportal glycogen, and reduced nephrocalcinosis and associated renal pathology were said to be due to reduced food intake in rats of this strain and age as observed historically; the majority of animals in the 0.5 - 2.0% dose groups exhibited caecal enlargement and pallor of the caecal contents
Test method:	not specified
Result:	no target organ was identified in a 3-week feeding study in rats at doses up to 2.0% of the notified chemical in the diet

9.2.2 13 week feeding study in rats (4)

Species/strain:	rat/ Wistar
Number/sex of animals:	10 males and 10 females per dose group
Method of administration:	dietary
Dose/Study duration::	doses of 0, 0.07%, 0.14%, 0.7% and 1.4% for 13 weeks
Clinical observations:	all animals survived in good health until the end of the trial
Clinical chemistry/Haematology	significantly higher cholesterol levels in both sexes at 1.4% and also in male rats at 0.7% test article; significantly higher total protein for male rats fed 1.4%; no significant effects on urinalysis or haematological parameters were observed
Histopathology:	both male and female rats fed 1.4% and male rats fed 0.7% test article exhibited significantly higher relative liver and kidney weights; centrilobular hypertrophy was observed in male rats of the high dose group together with enlargement of centrilobular hepatocytes and compression of adjacent sinusoids; this was suggested to be a reflection of cellular adaptation to increased metabolic load; in the kidneys in the high dose groups of males and females the intensity of spontaneous background pathology was slightly aggravated and in males increased numbers of hyaline droplets were observed in the proximal convoluted tubules probably related to disposal of absorbed protein; caecal enlargement and pallor of the caecal contents were recorded in the majority of rats fed 0.7 or 1.4% of the test article
Test method:	not specified
Result:	the major target organs were identified as the liver and kidney with a NOEL of 100 mg/kg/day

9.3 Metabolism on porcine skin (5)

Enzymatic hydrolysis of the notified chemical on epidermal slices of porcine skin was measured by gas liquid chromatographic analysis of hexane extracts for the presence of menthol, a hydrolysis product.

Slices of skin (5 cm^2) were exposed to the notified chemical at 2.5 mg/mL at 37°C in 0.01 M phosphate buffered saline. Negative controls included boiled skin to inactivate enzymes and buffer alone. A positive control of porcine pancreatic lipase was also included.

The rate of hydrolysis of the notified chemical in the presence of porcine skin was approximately 6 $\mu g/hour/cm^2$ compared to 1.1 $\mu g/hour/cm^2$ for boiled skin and 0.8 $\mu g/hour/cm^2$ for buffer alone. The positive control gave a hydrolysis rate of 2.8 $\mu g/hour/cm^2$.

Over 24 hours in the presence of skin the overall level of extractable menthol and of the notified chemical decreased by approximately 44%.

9.4 Overall Assessment of Toxicological Data

The notified chemical exhibited low acute oral toxicity to rats (LD_{50} > 9.6 g/kg) and mice (LD_{50} > 4.5 g/kg). In a 90-day repeat dose dietary feeding study the liver and kidney were identified as the target organs with a NOEL estimated at 100 mg/kg/day. The notified chemical was found not to be a skin sensitiser.

Although no irritation studies were submitted, the notifier anticipates that the notified chemical will irritate the eyes based on its cooling effect. A product dossier submitted with the notification states that the notified chemical as a concentration of 20% in acetone does not cause skin irritation (species unknown). The molecular weight of the notified chemical is 267, so both it and its metabolites could be absorbed across biological membranes.

The notifier states that pyrrolidone carboxylic acid, one of the two dermal metabolites of the notified chemical is a normal constituent of healthy skin, in which it is a moisturising factor, and as a result no toxicological hazard is anticipated.

The other dermal metabolite of the notified chemical, menthol, is a natural constituent of peppermint oil, and is used in soaps, detergents, creams, lotions and perfumes at a maximum concentration of 0.3%. Information on the toxicological profile was provided by the notifier (as an RIFM monograph) and has also been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (6). A summary of this information follows. Menthol is approved for food use by the US FDA and was assigned an ADI of 0-0.2 mg/kg/d by JECFA, based on a 5-week rat dietary study in which there were no treatment-related effects at the highest dose of 200 mg/kg/d l- or dl-menthol. Both isomers of menthol have acute oral LD_{50}s of approximately 3 000 mg/kg in rats and 800-1 600 mg/kg in cats. An acute dermal LD_{50} of

> 5 000 mg/kg was obtained with l-menthol in rabbits. When applied for 24 hr to the occluded intact or abraded rabbit skin, l-menthol did not cause irritation. Negative results were obtained with 8% l-menthol in petrolatum in a 48-hr closed patch test for dermal irritation in humans. No skin sensitisation occurred in a maximisation test performed on 24 volunteers with 8% menthol in petrolatum. However, occasional cases of urticaria and idiopathic auricular fibrillation have been reported among humans, arising from consumption of or dermal contact with l-menthol. Menthol was devoid of genotoxicity when tested in bacteria, in host mediated assays using bacteria and *Saccharomyces* as indicators, and in cytogenetic studies *in vitro* and *in vivo*.

The notified chemical would not be classified as hazardous according to Worksafe Australia's *Approved Criteria for Classifying Hazardous Substances* (7).

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

For new chemicals with import volumes under 1 tonne per annum, ecotoxicity tests are not required under the Act.

While no tests were submitted, ASTER provides a 96 h acute LC_{50} = 6.8 mg/L calculated value for Fathead minnow (*Pimephales promelas*). While this figure indicates the notified chemical is moderately toxic to fish, with only one result, no firm conclusions can be drawn with respect to fish or other aquatic species. Calculated results can be variable and should be used as a guide only.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The notified chemical is unlikely to present a hazard to the environment either during reformulation into cosmetic products, or end use when consumers wash the polymer residue to sewer after use or dispose of containers.

A worst case predicted environmental concentration (PEC) for reformulation has been derived using the following assumptions:

1. All reformulation and repacking is carried out at one site.

2. All release is to sewer (250 ML per day), where no degradation/hydrolysis occurs.

3. 1% of the total import volume (1 tonne) is released over 200 days of the year.

Using these assumptions, a PEC due to reformulation, prior to release to receiving waters, is 0.2 µg/L. This is several orders of magnitude below the calculated LC50 = 6.8 mg/L for Fathead minnow provided by ASTER.

End use of the product will result in a wide dispersive release over the continent. To determine a PEC based on end use release, the following assumptions have been

made:

1. All release is to sewer, where no degradation/hydrolysis occurs.

2. Sewer output per day is 2,700 ML, based on an Australian population of 18 million, and a daily per capita water usage volume of 150 L.

3. 98.5% of the total import volume (1 tonne) is released over 300 days of the year, giving a daily release of the notified chemical of 3.3 kg.

Using these assumptions, a continental PEC due to end use, prior to release to receiving waters, is 1.2 µg/L. This is several orders of magnitude below the calculated LC_{50} = 6.8 mg/L for Fathead minnow provided by ASTER.

Both local and continental predicted environmental concentrations support the conclusion of a low hazard.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

Both the notified chemical and its dermal metabolites, pyrrolidone carboxylic acid and menthol, are of sufficiently low molecular weight to penetrate the skin and other biological membranes, and hence are available for systemic absorption.

Based on the toxicological data provided the notified chemical is likely to exhibit low acute toxicity and is not likely to be a skin sensitiser. Effects on the liver and kidney may occur after repeated or prolonged exposure. However the notified chemical would not be classified as hazardous according to Worksafe Australia's *Approved Criteria for Classifying Hazardous Substances* (7) in relation to acute oral effects, severe effects after repeated or prolonged exposure and skin sensitising effects.

Exposure of workers to the notified chemical during transport and storage is only expected in the rare event of an accident in which case inhalation of the pure chemical in the form of a fine dust may occur. Exposure of workers during compounding of cosmetics is expected to be low. The concentration of chemical in cosmetic formulations will not exceed 3% with a maximum of about 2.0 kg to be added per batch.

Significant public exposure to the notified chemical will arise, primarily from its use in cosmetics. Consumers may be exposed dermally to the notified chemical for prolonged periods at concentrations of up to 3%. If 1 mL of a 3% preparation were applied per day, the amount of the notified chemical would be 30 mg. Assuming a body weight of 30 kg, in the case of a young adolescent, this would represent a dose of 1 mg/kg/d, or one hundredth of the oral NOEL for the notified chemical. In practice, the safety factor would probably be higher, given that absorption through the skin is likely to be less extensive than via the oral route.

It is anticipated that the notified chemical and its dermal metabolite, menthol, will not pose any significant systemic toxicological hazard to consumers when used in cosmetics as outlined by the notifier. No toxicological hazard is expected to arise

from the remaining dermal metabolite, pyrrolidone carboxylic acid, given that it is a natural constituent of skin.

The occupational health risk in manufacturing cosmetic formulations containing the notified chemical is expected to be low given the toxicological data provided and likely low exposure. However, given that the notified chemical is imported as a fine powder, local exhaust ventilation should be used during formulation.

13. RECOMMENDATIONS

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

- Good general and local exhaust ventilation should be provided in workplaces where compounding into cosmetics occurs and particularly during weighing out and transfer operations;
- Safety goggles should be selected and fitted in accordance with Australian Standard (AS) 1336 (8) to comply with Australian/New Zealand Standard (AS/NZS) 1337 (9);
- If engineering controls and work practices are not adequate to reduce inhalational exposure to a safe level then a mask conforming to Australian/New Zealand Standards 1715 (10) and 1716 (11) should be worn;
- Spillage of the notified chemical should be avoided, spillages should be cleaned up promptly and put into containers for disposal in accordance with Federal, State and Local government regulations;
- Good personal hygiene should be practised to minimise the potential for ingestion;
- A copy of the relevant Material Safety Data Sheet (MSDS) should be easily accessible to employees.

14. 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* (12).

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

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

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

specific conditions are prescribed.

16. REFERENCES

1. Russom C L, Anderson E B, Greenwood B E, Pilli A, 1991, 'ASTER: An integration of the AQUIRE database and the QSAR system for the use in ecological risk assessment', *Sci. Total Environ.* **109/110:**667-670.

2. Edwards K B *et al.*, 1977, *Biological Safety Evaluation of Menthyl Pyrrolidone Carboxylate (CF 76). Part 1. Acute and Subacute Oral Toxicity (3 weeks) to Colworth Wistar Rats*, Project No. 77 1377, Unilever Research Bedford, U K.

3. Long D, 1994, *Menthyl Pyrrolidone Carboxylate: Acute Oral Toxicity and Skin Sensitisation Studies*, Project Nos. MT 1700, SS 74.80, SS 75.173 and SS 75.297, Unilever Research Bedford, U K.

4. Edwards K B *et al.*, 1977, *Biological Safety Evaluation of Menthyl Pyrrolidone Carboxylate (CF 76). Part 2. Subacute Oral Toxicity (13 weeks) to Colworth Wistar Rats*, Project No. 77 1376, Unilever Research Bedford, U K.

5. Sanders D and Howes D, 1993, *The Fate of Menthyl Pyrrolidone Carboxylic Acid (MPC) in Porcine Skin in vitro*, Project No. AE930427, Unilever Research Bedford, U K.

6. Joint FAO/WHO Expert Committee on Food Additives, 1976, *Toxicological Evaluation of Certain Food Additives*, Twentieth Report of the JECFA, WHO Food Additives Series No. 10.

7. National Occupational Health and Safety Commission 1994, *Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(1994)]*, Australian Government Publishing Service, Canberra.

8. Standards Australia, 1994, *Australian Standard 1336-1994, Recommended Practices for Eye Protection in the Industrial Environment*, Standards Association of Australia Publ., Sydney.

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

10. Standards Australia, Standards New Zealand, 1994, *Australian/New Zealand Standard 1715 - 1994 Selection, Use and Maintenance of Respiratory Protective Devices*, Standards Association of Australia Publ., Sydney, Australia, Standards Association of New Zealand Publ., Wellington, New Zealand.

11. Standards Australia, Standards New Zealand,1991, *Australian/New Zealand Standard 1716 - 1991 Respiratory Protective Devices,* Standards Association

of Australia Publ., Sydney, Australia, Standards Association of New Zealand Publ., Wellington, New Zealand.

12. National Occupational Health and Safety Commission 1994, *National Code of Practice for the Preparation of Material Safety Data Sheets [NOHSC:2011(1994)]*, AGPS, Canberra.