File No: NA/329

Date: 12th January 1996

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

Hydroxylated Milk Glycerides

This Assessment has been compiled in accordance with the provisions of *the Industrial Chemicals (Notification and Assessment) Act 1989,* and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by Worksafe Australia which also conducts the occupational health & safety assessment. The assessment of environmental hazard is conducted by the Department of the Environment, Sport, and Territories and the assessment of public health is conducted by the Department of Human Services and Health.

For the purposes of subsection 78(1) of the Act, copies of this full public report may be inspected by the public at the Library, Worksafe Australia, 92-94 Parramatta Road, Camperdown NSW 2050, between the hours of 10.00 a.m. and 12.00 noon and 2.00 p.m. and 4.00 p.m. each week day except on public holidays.

For Enquiries please contact the Administration Coordinator at:

Street Address: 92 Parramatta Rd Camperdown, NSW 2050, AUSTRALIA
Postal Address: GPO Box 58, Sydney 2001, AUSTRALIA
Telephone: (61) (02) 565-9466 **FAX (61) (02) 565-9465**

Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

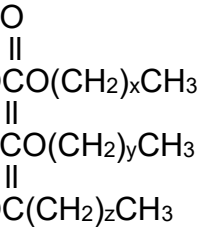
Hydroxylated Milk Glycerides

1. APPLICANT

Bronson and Jacobs Pty. Ltd. Parkview Drive, Australia Centre, Homebush, NSW, 2140 has submitted a standard notification statement in support of their application for an assessment certificate for hydroxylated milk glycerides.

2. IDENTITY OF THE CHEMICAL

Based on the nature of the chemical and the data provided, hydroxylated milk glycerides, is not considered to be hazardous.

Chemical name:	Hydroxylated milk glycerides
Chemical Abstracts Service (CAS) registry number:	144635-07-4
Other name:	Hydroxylated glycerides
Trade name:	Cremerol HMG
Molecular formula:	The glyceride is a combination of short, medium and long chain fatty acids. The vast majority are long chain fatty acids, with carbon lengths of 16 (palmitic) and 18 (steric) being the most abundant.
Structural formula: (General structure)	
Molecular weight:	A complex mixture with a range of molecular weights. The EPA has calculated the molecular weights of palmitic (x,y,z= 14) and stearic (x,y,z= 16) to be 807 and 891 respectively.

Method of detection and determination:

No quantitative method for analysis has been developed. Qualitative identification - Infrared spectra and NMR spectra were provided.

Spectral data:

IR: Major characteristic peaks and their functional group assignment are tabulated below:

Absorbance Band Frequency cm^{-1}	Functional Group Assignment
3466	0-H stretch
2924	CH_2 asymmetric stretch
2852	CH_2 symmetric stretch
1745	C=O stretch
1464	CH_2 deformation
1170	C-C-O asymmetric stretch
1105	O-CH_2-C asymmetric stretch
721	$(CH_2)_x$ C-H

The spectrum is consistent with a hydroxylated saturated triglyceride.

NMR: A proton NMR spectrum was provided and was consistent with the expected structure of the chemical with appropriate chemical shifts.

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	Soft white solid
Odour:	Milk fat
Melting Point:	40^0C
Glass-transition Temperature:	Unknown
Density:	0.97 g/cm^3 @ 20^oC
Vapour Pressure:	1.8 ± 0.02 x 10^{-3} mm Hg
Water Solubility:	Below detectable limits at 20^0C, <1mg.L^{-1}
Partition Co-efficient (n-octanol/water)	log $P_{o/w} \geq 5.3$
Hydrolysis as a function of pH:	Not given
Adsorption/Desorption:	Unknown
Dissociation Constant	Not applicable. there are no ionisable hydrogens and a dissociation constant is not expected.

Flammability Limits:	Could not be ignited with a flame. The test substance melted.
Combustion Products:	Unknown
Pyrolysis Products:	Unknown
Decomposition Temperature:	Unknown
Decomposition Products:	Unknown
Autoignition Temperature:	Minimum temperature for autoignition is 405^0C.
Explosive Properties:	Not explosive
Reactivity/Stability:	The notifier has stated that the product will not react exothermically with flammable material.
Particle size distribution:	Not applicable

Comments on physico-chemical properties:

All laboratory tests were carried out under OECD Good Laboratory Practice Guidelines, and according to the requirements of EEC Directives 92/69.

Water solubility of the chemical was determined based on a preliminary test for surface tension. The solubility in water is expected to be much less then 1 mg/L.

Hydrolysis as a function of pH was not applicable presumably due to the low solubility in water. The notified compounds contains ester functionalities that are expected to hydrolyse but this will be very slow under environmental conditions due to the low solubility in water.

Adsorption/desorption was not determined but the notified substance may be expected to attach to the organic fraction in soil.

As the notified chemical is a soft solid at 20^{o}C, does not form a powder or produce fines and forms a liquid at 40^{o}C, particle size was not considered applicable.

4. PURITY OF THE CHEMICAL

Degree of purity:	Minimum 99% pure
Toxic or hazardous impurity/impurities:	None
Non-hazardous impurity/impurities:	Moisture and ash
Maximum content of residual monomer(s):	Not Applicable
Additive(s)/Adjuvant(s):	None

5. INDUSTRIAL USE

Imports of the notified substance are estimated to reach 2.5 to 3.0 tonnes in 1999 from an initial 1 to 1.5 tonnes in 1996. It is to be imported containerised or in 250 L stainless steel drums or polyethylene pails of 25 L. These containers are designed to withstand impact.

Hydroxylated milk glycerides will be used as an emollient in liquid or lotion cosmetics such as skin care products at a concentration of 3-5% in packages of up to 500 mL in size. Most use is expected to take place in bathrooms or similar wet areas that drain to the sewer.

6. OCCUPATIONAL EXPOSURE

The notified chemical will be imported into the country in closed unbreakable containers. Inside the formulation facility it will be stored and transported in closed polyethylene pails or stainless steel drums. Mixing and dispensing of the notified chemical will be carried out in a closed system, or in one designed not to create aerosols or vapour hazard.

Six workers will be exposed to the notified chemical during handling, sampling, dispensing and mixing. The categories and numbers of workers are:

- 2 handlers/formulators who will handle the containers of the substance and prepare mixtures containing the notified chemical.
- 2 testers who will sample the formulations containing the notified chemical.
- 2 packers who will dispense and pack the formulated product.

Apart from the initial addition of hydroxylated milk glycerides, the formulations will be mixed and dispensed in closed systems or use equipment that minimises the formation of vapours or aerosols. Worker exposure is therefore quite limited. Exposure to the unformulated notified chemical will be for 4 hr/year for the handlers/formulators. Exposure of workers to the formulated product containing the notified chemical will vary between 2 and 4 days/year for the testers and packers.

7. PUBLIC EXPOSURE

The notified chemical, Cremerol HMG, an hydroxylated milk glyceride prepared through hydroxylation of the lipid fraction of milk, will be imported into Australia at the rate of 500 kg to 1 tonne in 1995; 1 to 1.5 tonnes in 1996; 1.5 to 2 tonnes in 1997; 2 to 2.5 tonnes in 1998, and 2.5 to 3 tonnes in 1999. The chemical will be used as an emollient in liquid or lotion cosmetics. The notifier estimates that the chemical will be incorporated at a concentration of 3-5% in packages up to 500 mL.

Widespread dermal, and possible ocular exposure, will result from use of cosmetics which incorporate the notified chemical. Minor public exposure may result from accidental spillage during transport and storage of the emollient.

8. ENVIRONMENTAL EXPOSURE

Release

Release to the environment during the transport and storage of the product would be confined to breakages from transport accidents. Release from the imported

containers is expected to be rare. Formulation and dispensing is to be done in closed systems which are largely automated, therefore minimising possible spills. Any spills that do occur during transport or formulation are to be treated according to instructions in the MSDS sheets. These are to collect spill solids and adsorb solution. Disposal of spilt material is to be by landfill.

Release to the environment from use would be when the cosmetics containing the chemical are washed or wiped off the face and hands and residues in “empty” containers are disposed of. The volume released to the waste stream has not been stated by the notifier but it is estimated by the EPA that most of the imported material could be released to the sewer. The remainder is expected to be widely dispersed throughout the environment during use or disposed of with the ‘empty containers’ and be consigned with the household garbage to be landfilled or incineration.

Fate

The fate of most of the notified chemical is disposal via the sewer when consumers wash off cosmetics. The notified chemical did not meet the stringent criteria for readily biodegradable. However, 74% degradation did occur after 28 days, therefore significant degradation of the chemical is expected during the process through the sewage system.

Any remaining chemical is expected to be disposed of with the household garbage the final fate being incineration or landfill. Any spills that occur during transport or formulation are treated according to the MSDS and disposed of by landfill. In landfill the chemical is expected to degrade, similar to other biological material. Incineration will produce the normal products of combustion (oxides of carbon and water).

Bioaccumulation is not expected due to the degradation which will limit the bioaccumulation potential.

9. EVALUATION OF TOXICOLOGICAL DATA

9.1 Acute Toxicity

Table 1. Summary of the acute toxicity of hydroxylated milk glycerides

Test	Species	Outcome	Reference
Acute oral toxicity	Rat	LD_{50} >16 g/kg	(1)
Acute dermal toxicity	Rabbit	LD_{50} >16 g/kg	(1)
Skin irritation	Rabbit	moderate irritant	(1)
Eye irritation	Rabbit	slight irritant	(1)
Skin sensitisation	Guinea pig	negative	(2)

9.1.1 Oral Toxicity (1)

Sprague Dawley rats (approximately 7-12 weeks old) were administered either 16 g (n = 5 per sex) or 8 g (n = 5 per sex) of hydroxylated milk glycerides in corn oil/kg by a single gavage dose. The animals were maintained for 14 days. Mortality, and clinical signs of toxicity, were assessed frequently during day 1, and twice daily thereafter. Body weight was determined on days 1 (pre-dosing), 7 and 14. An

autopsy was performed at the completion of the study, and selected organs were preserved for histology.

No deaths were recorded during the study. Diarrhoea, brown staining of the perineal and/or perianal region, crusts around the perianal region, and greasy fur were often noted for the first 4-5 days of the study.

The acute oral LD50 of the notified chemical was greater than 16 g/kg in male and female rats.

9.1.2 Dermal Toxicity (1)

A dose of 16 g/kg of hydroxylated milk glycerides was applied to shaved, intact skin of New Zealand White rabbits (5 per sex, approximately 13-18 weeks old). The area was occluded for 24 hours. The study was terminated after 14 days. Mortality, and clinical signs of toxicity, were assessed frequently during test day 1, and twice daily thereafter. Body weight was determined on days 1 (pre-dosing), 7 and 14. An autopsy was performed on all animals at the completion of the study, and selected organs preserved for histopathology.

No deaths were recorded during the study. Erythema and oedema were noted in all animals on test day 1, and desquamation was noted in 1 of 5 males and 4 of 5 females on test day 7, and 2 of 5 females on test day 14.

The acute dermal LD50 of the notified chemical was greater than 16 g/kg in male and female rabbits, and the notified chemical showed moderate dermal irritation.

9.1.3 Inhalation Toxicity (1)

A group of Sprague Dawley rats (5 per sex; approximately 7-12 weeks old) were placed in a 120 litre chamber in which 123.5 g of hydroxylated milk glycerides had been placed 21 hours previously. This produced a "saturated" vapour in the chamber according to the study report. The animals were removed after 6 hours. The study was terminated after 14 days. Mortality, and clinical signs of toxicity, were assessed frequently during test day 1, and twice daily thereafter. Body weight was determined on days 1 (pre-exposure), 7 and 14. An autopsy was performed on all animals at the completion of the study.

No deaths, signs of toxicity, or gross lesions were noted during the study.

9.1.4 Skin Irritation (1)

The fur was removed from the back of 6 New Zealand White rabbits (3 per sex; 14-15 weeks old), and 500 mg of hydroxylated milk glycerides was applied to the intact skin for 4 hours. Residual chemical was then removed. The study was terminated after 14 days. Skin reactions were assessed 1, 24, 48 and 72 hours and at days 7 and 14 after chemical removal. The severity of the reactions were determined by the degree of erythema, eschar formation and oedema according to the method of Draize.

Slight erythema was noted in all animals after 1 hour (mean score 1), and in 2 of 3 males after 24, 48, 72 hours and after 7 days (mean score 0.3-0.5). Slight oedema was noted after 24 hours in 4 of 6 animals (mean score 0.7) which resolved within 48 hours. Within 7 days, fissuring was noted in 1 of 6 animals, and desquamation was noted in 3 of 6 animals.

The notified chemical is not determined to be a hazardous substance nor classified as “Irritant” as the scores are below the threshold. If the erythema and oedema induced by the notified chemical are considered alone, the substance would be considered a slight dermal irritant. However, in light of the desquamation in 50% of the test animals, and fissuring in one animal 7 days after the chemical application, the notified chemical is considered a moderate irritant.

9.1.5 Eye Irritation (1)

A dose of approximately 100 mg of hydroxylated milk glycerides was instilled into the conjunctival sac of 4 New Zealand White rabbits (2 per sex). The contralateral eye acted as a control. The study was terminated after 7 days. The eyes were examined 1, 24, 48 and 72 hours, and 7 days after chemical instillation, and the degree of corneal, iridic and conjunctival irritation assessed as described by Draize. Corneal epithelium disruption was assessed using fluorescein.

One hour after chemical installation, slight conjunctival erythema and ocular discharge was noted in all animals (mean score 1). The discharge resolved, although the erythema remained evident (mean score 0.8) for 48 hours in 3 of 4 animals. Total mean Draize score after 1 hour was 4, after 24 hours was 2.5, and after 48 hours was 1.5.

The notified chemical was a slight ocular irritant in rabbits.

9.1.6 Skin Sensitisation (2)

Five female Himalayan albino guinea pigs (5-6 weeks old) were used in a preliminary induction dose finding study. Subsequently, 15 female Himalayan albino guinea pigs were divided into a control (n = 5) and a treatment group (n = 10). The hair was removed, using clippers, from a region over the scapular. The induction doses consisted of a series of intradermal injections given either side of the clipped area on test day 1. The intradermal injections were either hydroxylated milk glycerides dissolved to 2.5% (w/w) with corn oil, 50:50 Freunds Complete Adjuvant with water, or 50:50 hydroxylated milk glycerides dissolved to 5% with corn oil:Freunds Complete Adjuvant. On test day 7 the clipped scapular area was rubbed with 10% sodium-dodecyl-sulfate. On test day 8, an epidermal induction dose of 0.5 mL of a 50% w/w suspension of the notified chemical (hydroxylated milk glycerides) in corn oil was applied to the exposed skin of the treatment group. An occlusive dressing was applied, and after 48 hours the chemical, and dressing, were removed. Application sites were assessed for erythema and oedema following removal of the dressing. The control group was treated in a similar fashion to that described, but the notified chemical was omitted. The challenge dose for each animal was applied epidermally to the shaved regions and consisted of 0.05 mL of a 10%, 25% and 50% suspension of the notified chemical (hydroxylated milk glycerides) in corn oil. The residual test material was removed after 24 hours. The application sites were assessed for redness and swelling 24 and 48 hours after removal of the test material. In addition, animals were examined for clinical signs of toxicity on a daily basis, and body weights were determined at the beginning and end of the study.

In response to the challenge dose, 1 of 10 animals (10%) showed discrete or patchy erythema in response to the 10%, 25% and 50% test substance concentrations.

The notified chemical is not considered to cause sensitisation in the guinea pig.

9.2 Repeated Dose Toxicity (3)

Groups of Wistar rats (5 per sex; approximately 6 weeks old) were administered 0, 50 mg (LD), 200 mg (MD) or 1000 mg (HD) of hydroxylated milk glycerides (in corn oil)/kg/day, by gavage, for 30 days. Clinical signs of toxicity were assessed daily, and animal viability was assessed twice daily, food consumption and body weight was determined weekly, and an ophthalmic examination was carried out during the final week of the study. Blood was collected for haematology and clinical biochemistry at the completion of the study. Autopsies, which included selected organ histology, and weight determination, were carried out at study termination.

No treatment related effects were noted (clinical signs, bodyweight variation, food consumption, opthalmoscope examination, haematology, clinical biochemistry, or pathology) during the study.

9.3 Genotoxicity

Summary of genotoxicity studies using hydroxylated milk glycerides:

STUDY TYPE	TEST OBJECT	CONCENTRATION	RESULT	REF.
Reverse mutation	*S. typhimurium* strain TA98, TA100, TA 1535, TA1538	0.1-10.0 mg/plate (± rat liver S9 fraction activation)	-ve	4
In vitro mutageni-city	Human lymphocyte	33, 100 and 200 mg/kg (± rat liver S9 fraction activation)	-ve	5

No evidence of mutagenic activity with 5 strains of *Salmonella typhimurium* with and without S9 metabolic activation. There was no evidence of clastogenesis in the study using cultured peripheral human lymphocytes.

9.4 Overall Assessment of Toxicological Data

The studies demonstrated that the notified chemical (hydroxylated milk glycerides) has low acute oral and dermal toxicity, is a moderate dermal and a slight ocular irritant, but does not cause dermal sensitisation. The concentration of the chemical which was inhaled during the acute inhalation toxicity study was not measured, and as such, no definitive conclusions can be drawn from the results obtained. A 30 day repeat dose study in rats showed no significant chemical related effects. The compound, when assessed in *in vitro* test systems, was not mutagenic or clastogenic.

On the basis of the available toxicological data the notified chemical, hydroxylated milk glycerides would not be classified as hazardous according to the criteria of Worksafe Australia (6).

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

Ecotoxicity studies were provided by the notifier. A detergent (Tween-80) was used to increase the solubility of the notified chemical.

The results for fish, daphnia and algae indicate the notified chemical is practically non-toxic, slightly toxic and slightly toxic respectively. As these results were higher than the expected solubility, significant effects on aquatic organisms are not expected when the chemical is released to waterways.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

Most of the notified chemical is expected to be disposed of to the sewer after use. The Commonwealth EPA's calculations show that there should be no hazard to aquatic organisms from these discharges. During treatment of the sewage in the treatment works, some of the notified chemical is expected to degrade, with the remainder being associated with the sludge, due to the high log P and low solubility. These sludges from sewage treatment works are normally either incinerated or landfilled.

As the chemical has low solubility in water, it will not leach when consigned to landfill. In the landfill the notified chemical is expected to degrade like other fatty materials. The environmental hazard from the disposal of containers and sludges containing the notified chemical by landfill is rated as negligible.

The overall environmental hazard can be rated as negligible.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The notified chemical (hydroxylated milk glycerides) is an emollient to be used in cosmetics. Widespread dermal, and possibly ocular contact, will result during use of cosmetics which incorporate the notified chemical. The chemical is to be incorporated into cosmetics at a concentration of 3-5%, and as such, the potential for skin and eye irritation is unlikely. Since repeated oral dosing of rats did not reveal any form of toxicity, it is unlikely that dermal application at this concentration to humans would result in adverse effects.

13. RECOMMENDATIONS

To minimise occupational exposure to hydroxylated milk glycerides (pure form or during formulation) the following guidelines and precautions should be observed:

. if engineering controls and work practices are insufficient to reduce exposure of eyes and skin to hydroxylated milk glycerides to a safe level, then personal protective devices which conform to and are used in accordance with Australian Standards (AS) for eye protection (AS 1336, AS 1337) (7,8), impermeable gloves (AS 2161) (9) and protective clothing (AS 3765.1, 3765.2) (10,11) should be worn;

. a copy of the Material Safety Data Sheet should be easily accessible to employees.

14. MATERIAL SAFETY DATA SHEET

The Material Safety Data Sheet (MSDS) for hydroxylated milk glycerides was provided in Worksafe Australia format (12).

This MSDS was provided by Bronson & Jacobs Pty. Ltd. as part of their notification statement. The accuracy of this information remains the responsibility of Bronson & Jacobs Pty. Ltd.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the *Industrial Chemicals (Notification and Assessment) Act 1989*, secondary notification of hydroxylated milk glycerides 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. SM Christopher and RC Myers, 1993. *Cremerol HMG: Acute toxicity and primary irritancy testing using the rat (peroral and inhalation toxicity) and the rabbit (cutaneous and ocular tests).* Bushy Run Research Centre, Union Carbide Chemicals and Plastics Co. Inc, USA. Report no.: 93U1251, September 1993. GLP.

2. PAM Daamen, 1994. *Assessment of contact hypersensitivity to Cremerol HMG in the albino guinea pig*. Notox BV, The Netherlands. Project no.: 110328, June1994. GLP, QA.

3. ACM Schoemakers, 1994. *Subacute 28 day oral toxicity with Cremerol HMG by daily gavage in the rat*. Notox BV, The Netherlands. Project no.: 110317, May 1994. GLP, QA.

4. JS Verges and ER Morabit**,** 1993. *Cremerol HMG: Mutagenic potential in the Salmonella/microsome (Ames) assay*. Bushy Run Research Centre, Union Carbide Chemicals and Plastics Co. Inc, USA. Report no.: 93U1258, August 1993. GLP.

5. EJ van de Waart, 1994. *Evaluation of the ability of Cremerol HMG to induce chromosome aberrations in cultured peripheral human lymphocytes*. Notox BV, The Netherlands. Project no.: 110339, June 1994. GLP, QA.

6. National Occupational Health and Safety Commission, 1994, *Approved Criteria for Classifying hazardous Substances [NOHSC:1008(1994)]*, AGPS, Canberra.

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

8. 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.

9. Standards Australia, 1987*, Australian Standard 2919 - 1987 Industrial Clothing*, Standards Association of Australia Publ., Sydney, Australia.

10. Standards Australia, 1978, *Australian Standard 2161-1978, Industrial Safety Gloves and Mittens (excluding Electrical and Medical Gloves),* Standards Association of Australia Publ., Sydney, Australia.

11. Standards Australia, Standards New Zealand 1994, *Australian/ New Zealand Standard 2210 - 1994 Occupational Protective Footwear, Part 1: Guide to Selection, Care and Use. Part 2: Specifications,* Standards Association of Australia Publ., Sydney, Australia, Standards Association of New Zealand Publ. Wellington, New Zealand.

12. National Occupational Health and Safety Commission, 1990*, Guidance Note for the Completion of a Material Safety Data Sheet,* 2nd. edition, AGPS, Canberra.