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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

[17-(2-FURANYL)-8, 11-CIS, CIS HEPTADECADIENE]

(AVOCATIN 302)

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

[17-(2-FURANYL)-8, 11-CIS, CIS HEPTADECADIENE]

(AVOCATIN 302)

1. APPLICANT

Reliv Australia Pty Ltd of Level 2, 80 Phillip Street, Parramatta NSW 2150 have submitted a limited notification for the assessment of Avocatin 302.

2. IDENTITY OF THE CHEMICAL

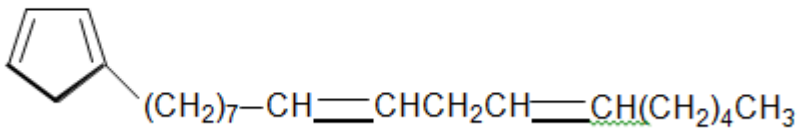
Chemical name: [17-(2-furanyl)-8, 11-cis, cis heptadecadiene]

Chemical Abstracts Service (CAS) Registry No.: 148675-93-8

Other names: Avocatin 302
Reavo
MW302
CH214598

Molecular formula: $C_{21}H_{34}O$

Structural formula:



Molecular weight: 302

Method of detection and determination:

The chemical can be isolated by HPLC and determined by infra-red spectroscopy and quantitatively determined by UV/Visble spectral analysis.

Spectral data:

Infrared spectrum (Kbr): Major characteristic peaks were observed at 726.5, 1009.9, 1148.1, 1463.9, 1655.9, 2854.8, 2926.2 and 3008.7 cm^{-1}.

UV/Visible spectrum: A broad absorbance band was observed with characteristic peak at 216 nm .

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	Pale to medium yellow oily liquid
Boiling Point:	> 60°C
Density:	870.8 kg/m^3 at 25°C
Vapour Pressure:	Not determined
Water Solubility:	Insoluble (predicted)
Partition Co-efficient (n-octanol/water) log P_{ow}:	Not determined
Hydrolysis as a function of pH:	Not supplied
Adsorption/Desorption:	Not determined
Dissociation Constant pK_a**:**	Not determined
Flammability Limits:	Not flammable
Autoignition Temperature:	Not determined
Explosive Properties:	None
Reactivity/Stability:	Not reactive
Flash Point:	> 82°C
Particle size distribution:	Not applicable

4. PURITY OF THE CHEMICAL

Degree of purity: > 99%

Hazardous impurities:

. **Chemical name:** Mixed furans
Weight percentage: < 0.1%

Non-hazardous impurities (> 1% by weight): none

Additive(s)/Adjuvant(s): BHA or BHT or Propyl Gallate as antioxidants.

. Comments on physico-chemical properties

Vapour pressure data could not be ascertained as the chemical polymerised before the output of vapour could be detected.

Water solubility of the chemical was impossible to determine as it demonstrated a poor ability to form a continuous phase with water. Emulsions formed were also unstable. The literature (2), states that, *long straight chain hydrocarbons have very low aqueous solubilities*.

Hydrolysis as a function of pH is not supplied. The notified substance as imported in the cosmetic formulation is in a neutral pH suspension with anti oxidant protection (vitamin E). It is suspected from the structure that the notified substance would breakdown when subjected to high pH conditions but these conditions are not likely to be encountered during the normal life and use of the cosmetic formulation. However, this attribute may aid in breakdown and degradation in the waste stream.

Partition coefficient could not be determined because of the insolubility in water of the notified substance, but would be expected to be relatively high.

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

5. INDUSTRIAL USE

The notified chemical will used as a moisturizing agent, as a component of a formulated cosmetic skin cream at a level of 3% by weight. The product will be imported in ready to use 70 mL plastic jars to Australia at the rate of 25000 kg per annum which is equivalent to 750 kg of Avocatin 302. The main site of use is in the domestic bathroom or dressing room. The facial cream containing the notified chemical is applied in small quantities to the face and massaged until adsorbed to the skin.

6. OCCUPATIONAL EXPOSURE

Avocatin 302 as a component of a skin cream formulation, will be imported at a rate of 750 kg per annum of Avocatin 302. Only the final finished product, fully packed as individual units will be imported to Australia. The product containing the notified chemical will be handled only by dockyard and transport workers, retail staff and storemen. The exposure to the notified chemical may occur only in the event of an accidental spillage.

7. PUBLIC EXPOSURE

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 of the product which contains the notified chemical during transport and storage.

8. ENVIRONMENTAL EXPOSURE

. Release

Release to the environment during the transport and storage of the product would be confined to breakages from transport accidents. The release would be limited in size by the low volume contained in the individual packs (70 mL). Spills would be contained then picked up on adsorbent material and consigned to landfill. Considerably less than 1 tonne of face cream (30 kg of the notified substance) is likely to be released in this manner.

Release to the environment from use would be in residues of the cream washed or wiped off the face and hands and residues in used "empty" containers. The volume released to the waste stream is stated by the notifier as not to exceed 500 kg per annum or 70% of the quantity imported. This quantity would be widely distributed in the sewer systems of the cities and towns of Australia. The empty bottles containing some small quantity of residue would be consigned with the household garbage to landfill or incineration.

. Fate

Precise details of the fate of Avocatin 302 in the environment are not known. The notifier states that it would be expected to behave as a vegetable oil and be degraded in the sewerage treatment process or in landfill by oxidation and microbial breakdown. The furan component of the chemical is expected to undergo hydroxylation under aerobic or anaerobic conditions (1). For the long straight chain component of the chemical these are known to biodegrade rapidly (2). Should the import of the notified substance exceed 1 tonne biodegradation results should be provided as part of a Secondary Notification.

9. EVALUATION OF TOXICOLOGICAL DATA

No toxicological data are required for chemicals less than 1 tonne, according to the *Act*. However, the following studies were carried out on Avocatin 302 and are reported here.

9.1.1 In Vitro Percutaneous Absorption through Hairless Mouse Skin (3)

Result: Does not penetrate skin nor does it partition into receptor fluid

Species/strain: HRS/J type hairless mouse *Number of replicates: three*

Method: Avocatin 302 applied on the naked hairless skin

Dose: 100 μl *Effective surface area:* 0.6362 cm^2

9.1.2 Comparison of Inflammation/Irritation after Treatment with Increasing Doses of either Retinyl Palmitate or Avocatin 302 (4)

Result: Irritant Potential of 2% Avocatin 302 is comparable to 0.5% Retinyl palmitate.

Species/strain: Not specified

Number/sex of animals: 8-10 female hairless mice/group (7 groups)

Method : Mice skin was treated with 0.1 ml of the formulation each day for 14 days.

Dose: 1%, 2% and 3% of Avocatin; 0.1% and 0.5% Retinyl palmitate

Clinical observations: Mild to moderate dermal and subcuticular inflammation acanthosis

Mortality: None

Test Method: Not available

9.3 Genotoxicity

9.3.1 *Salmonella typhimurium* and *Escherichia Coli* Reverse Mutation Assay (5)

Result: not mutagenic

Comments: Avocatin 302 did not induce *Salmonella typhimurium* and *Escherichia coli* revertants when tested at concentrations ranging between 5000 and 312.5 μg/plate with or without metabolic activation. Treatment with positive controls resulted in a dose-related induction of revertants in the tester strains.

Strains: *Salmonella typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *Escherichia coli* WP2*uvrA*$^{-}$

Positive controls: N-ethyl-N'-nitro-N-nitrosoguanidine, 2-Nitrofluorene, 9-Aminoacridine

Metabolic activation: rat liver S9 *Solvent:* dimethylsulfoxide

Concentration range: 312.5 - 5000 μg/ plate

Test Method: Not specified

9.3.2 Induction of Mutation at the Thymidine Kinase Locus of Mouse Lymphoma Cells(6)

Result: Not mutagenic

Comments: Slight variation in mutagenic frequencies were observed related to the controls but had no dose response relationship as observed in the positive controls.

Positive controls: Ethylmethanesulfonate and 3-Methylcholanthrene

Cell cultures: The TK$^{+/-}$ cells, a subline of the mouse lymphoma cell (L5178Y)

Metabolic activation: Rat liver S9 *Solvent:* *D*imethylsulfoxide

Concentration range: 1,10,25, 50, 100, 150, 200 and 250 μg/ml

Test Method: Not specified

9.3.3 *In Vitro* Induction of Unscheduled DNA synthesis Cytogenetic Assay in Cultured Rat Hepatocytes (7)

Result: Avocatin 302 did not show induction of Unscheduled DNA synthesis with cultured adult hepatocytes.

Cell Culture:lCultured adult rat hepatocytes

Metabolic activation: Rat hepatocytes *Doses:* 1000, 500, 100, 50, 10, 5, 1 and 0.5 μg/ml

Positive controls: N-methyl-N' -nitro-N-nitrosoguanidine, 2-Acetylaminofluorene

Negative control: Dimethylsulfoxide

Comments: A dose related increase in UDS was observed with positive controls

Test Method: Not specified

9.3.2 *In Vivo* Sister Chromatid Exchange (SCE) in Bone Marrow of Chinese Hamsters (8)

Result No significant increase in the number of first division metaphase SCE were observed.

Time of exposure: 19 hours

Positive control:	*Cyclophosphamide*	*Doses: 50 (control only), 125, 250, 500 mg/kg*

Comments: The frequency of SCE when treated with the notified chemical was similar to the controls

Test Method Not specified

9.4 Overall Assessment of Toxicological Data

Avocatin 302 does not penetrate skin. Dermal irritant potential of Avocatin (2%) is comparable to Retinyl palmitate (0.5%). Avocatin 302 was found to be non-genotoxic: *in vitro* to *Salmonella typhimurim* TA 1535, TA 1537, TA 98 and TA 100 and Escherichia coli reverse mutation assay; *In vitro* to Mouse Lymphoma Thymidine Kinase assay and *in vivo* Induction of Unscheduled DNA synthesis in Human Lymphocytes.

On the basis of submitted data, Avocatin 302 cannot be classified as hazardous according to Worksafe Australia's Approved Criteria for Classifying Hazardous Substances () in relation to mutagenic effects.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

Ecotoxicological data were not provided, which is acceptable for low volume chemicals (< 1 tonne) according to the *Act*.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The import, use and disposal of Avocatin-302 should not pose a hazard to the environment when used as minor part of the formulation of a cosmetic facial cream. The volume of use is low and distribution to the waste stream is expected to be widespread across Australia and not likely to produce an undue load on the ability of sewerage treatment plants to treat and biodegrade effluent containing the notified substance.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

It is noted that the notified substance is imported as a skin cream formulation of which it constitutes 3% by weight. Spillage during transport is unlikely to be a source of exposure. Avocatin 302 does not penetrate skin and non-genotoxic.

Given the low intrinsic health hazard of the notified chemical together with expected low exposure, the occupational health risk arising from use is expected to be minimal.

Widespread dermal, and possibly ocular contact, will result during use of the skin creams which incorporate the notified chemical. Minor public exposure may result from accidental spillage of the product.

In view of the widespread dermal, and possible ocular exposure to the chemical, the limited information on the irritancy potential, and the unknown skin sensitisation activity, there is insufficient information to form a conclusion as to the public health implications of the use of the skin care product containing Avocatin 302.

13. RECOMMENDATIONS

To minimise occupational exposure to Avocatin 302 the following guidelines and precautions should be observed:

. in the event of a spill to reduce exposure of Avocatin 302 to a safe level, personal protective devices which conform to and are used in accordance with Australian Standards, impermeable gloves (AS 2161) (9) and overalls; and

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

. the product containing the notified chemical should carry the following statements on the label:

- Avoid contact with eyes, lips and mouth; and

- Do not use on broken skin, if skin becomes irritated discontinue use.

14. MATERIAL SAFETY DATA SHEET

The attached MSDS for the products containing Avocatin 302 was provided in a suitable format (10).

This MSDS were provided by Avocatin 302 as part of their notification statement. It is reproduced here as a matter of public record. The accuracy of this information remains the responsibility of Reliv Australia Pty Ltd.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the *Industrial Chemicals (Notification and Assessment) Act 1989*, secondary notification of Avocatin 302 shall be required if any of the circumstances stipulated under subsection 64(2) of the Act arise. Also secondary notification shall be required if importation of the notified chemical exceeds one tonne, and should provide all the Schedule data including biodegradation studies for a Standard Notification. If necessary physico-chemical properties such as water solubility and patition co-efficient should be estimated.

16. REFERENCES

1. Kuhn E P, and Suflita J M, *Microbial degradation of Nitrogen, Oxygen and Sulfur Heterocyclic Compounds Under Anaerobic Conditions: Studies with Aquifer Samples*. Environmental Toxicology and Chemistry, Vol 8, pp1149-1158, 1989.

2. Klopman G, Balthasar DM, and Rosenkranz H S, *Application of the Computer -Automated Structure Evaluation (CASE) Program to the Study of Structure -Biodegradation Relationships of Miscellaneous Chemicals* . Environmental Toxicology and Chemistry, Vol 12, pp231-240, 1993.

3. *In vitro* percutaneous absorption of Avocatin 302 through hairless mouse skin (Data on file).

4. Comparison of inflammation/irritation after treatment with increasing doses of either retinol palmitate or Avocatin 302 (Data on file).

5. Studies 870629AMT2937 and 870713AMS2937, August 1987. Induction of Reverse Mutations in *Salmonella typhimurium* and *Escherichia coli* using the Ames Test. Lilly Research Laboratories, Indiana, USA.

6. Studies 870715MLT2937 and 870722MLA2937, August 1987. The Effect of Avocatin 302 302 on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells. Lilly Research Laboratories, Indiana, USA.

7. Studies 870630UDS2937 and 870707UDS2937, July 1987. The Effect of Avocatin 302 on the Induction of DNA Repair Synthesis in Primary Culture of Adult Rat Hepatocytes. Lilly Research Laboratories, Indiana, USA.

8. Study 870713SCE2937, September 1987. The Effect of Avocatin 302 on the *in vivo* Induction of Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters. Lilly Research Laboratories, Indiana, USA.

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

10. Worksafe Australia, February 1990, Guidance Note for a Completion of a Material Safety Data Sheet, Australian Publishing Service, Canberra.