

## Final Report on the Safety Assessment of Stearyl Heptanoate<sup>1</sup>

**Abstract:** The ester Stearyl Heptanoate, a waxy solid that is insoluble in water, is used as a skin conditioning agent—occlusive in a wide variety of cosmetic formulations at varying concentrations (e.g., up to 25% in lip balms, up to 5% in ointments). Studies report a high oral LD<sub>50</sub>, >5 g/kg, for rats. Animal data indicate potential for mild skin irritation, but none for sensitization. Undiluted Stearyl Heptanoate did produce some ocular irritation in rabbits, but a 1.5% solution produced no effects. Mutagenesis assays (Ames and micronucleus test) were negative. Clinical data showed no evidence of irritation or sensitization or comedogenicity. Although animal and clinical sensitization studies were done at a low concentration compared with expected use concentrations, the data suggest that it would not be a sensitizer even at higher concentrations. Data on ocular irritation show only mild reactions to undiluted Stearyl Heptanoate, suggesting that expected use concentrations should not produce significant ocular irritation. On the basis of the available animal and clinical data, it is concluded that Stearyl Heptanoate is safe for use as a cosmetic ingredient in the present practice of use. **Key Words:** Stearyl Heptanoate—Skin irritation—Rat—Sensitization.

Stearyl Heptanoate is the ester of stearyl alcohol and heptanoic acid which functions as a skin conditioning agent—occlusive (Wenninger and McEwen, 1992). Data on a trade compound, PCL Solid 2/066220, which is a mixture of Stearyl Heptanoate and Stearyl Caprylate (Dragoco, 1993) are also included in this report. The concentration of Stearyl Heptanoate in PCL Solid 2/066220 is >50% (Pradhan, 1993).

Additionally, a final report on the safety assessment of Stearyl Alcohol has been issued by the CIR Expert Panel (Elder, 1985). Relevant data from the Stearyl Alcohol report and relevant published data obtained from a literature search on Stearyl Alcohol and heptanoic acid are summarized where applicable.

### CHEMISTRY

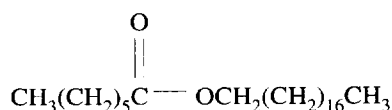
#### Definition and Structure

Stearyl Heptanoate (CAS No. 66009-41-4) generally conforms to the formula (Wenninger and McEwen, 1993):

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<sup>1</sup> Reviewed by the Cosmetic Ingredient Review Expert Panel.

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Stearyl Heptanoate is also known as Heptanoic Acid, Octadecyl Ester, and the tradenames Crodamol W, Prodhypore ST, and Tegosoft GH (Wenninger and McEwen, 1993). PCL Solid 2/066220 is the trade name of a mixture that contains Stearyl Heptanoate and Stearyl Caprylate (Pradhan, 1993).

### Physical and Chemical Properties

The chemical and physical nature of Stearyl Heptanoate resembles the preen gland secretions of ducks and other aquatic birds (Croda Inc., 1985). It is an off-white waxy solid that has a melting point of  $\sim 26^\circ\text{C}$ . Stearyl Heptanoate, as a 10% solution, is soluble in ethanol, mineral oil, corn oil, oleyl alcohol, and castor oil. It is not soluble in water (Croda Inc., 1991) or ethanol/water (90/10) (Croda Inc., 1985). The physical and chemical properties of Stearyl Heptanoate are summarized in Table 1.

PCL-Solid 2/066220 [composed of  $\geq 50\%$  Stearyl Heptanoate (Pradhan, 1994)]

TABLE 1. *Physical and chemical properties of Stearyl Heptanoate*

|   |   |   |
|---|---|---|
| Physical appearance<br>(at $25^\circ\text{C}$ ) | Waxy solid  | Croda Inc., 1985                                |
| Color   | Off-white   | Croda Inc., 1985                                |
| Odor  | Mild, characteristic  | Croda Inc., 1985                                |
| Empirical formula                               | $\text{C}_{25}\text{H}_{50}\text{O}_2$                                  | Wenninger and<br>McEwen, 1993                   |
| Molecular weight                                | 382.67  | Yakuji Nippo Ltd., 1987                         |
| Melting point                                   | $\sim 26^\circ\text{C}$   | Croda Inc., 1985                                |
| Boiling point                                   | $>400^\circ\text{F}$ ( $>204^\circ\text{C}$ )                           | Croda Inc., 1991                                |
| Specific gravity                                | $\sim 0.9$  | Croda Inc., 1991                                |
| Solubility (10% solution)                       | Soluble in ethanol, mineral oil, corn oil,<br>oleyl alcohol, castor oil | Croda Inc., 1985                                |
|   | Insoluble in ethanol/water (90/10)                                      | Croda Inc., 1985                                |
|   | Insoluble in water  | Croda Inc., 1991                                |
| Impurities                                      | $<1.5$ ppm chromium compounds   | Croda Inc., 1991                                |
|   | $<0.4$ ppm cadmium compounds  | Croda Inc., 1991                                |
|   | $<10$ ppm lead compounds  | Croda Inc., 1991                                |
|   | $<10$ ppm heavy metals  | Yakuji Nippo Ltd., 1987                         |
|   | $<1$ ppm arsenic  | Yakuji Nippo Ltd., 1987                         |
| Reactivity (stability)                          | Stable (at neutral pH)  | Croda Inc., 1991                                |
| % volatile by volume                            | $<1$  | Croda Inc., 1991                                |
| Flash point                                     | $>400^\circ\text{F}$ ( $>204^\circ\text{C}$ )                           | Croda Inc., 1991                                |
| Acid value                                      | 1.0 maximum   | Croda Inc., 1985 and<br>Yakuji Nippo Ltd., 1987 |
| Iodine value                                    | 2.0 maximum   | Croda Inc., 1985                                |
| Saponification value                            | 138–153   | Croda Inc., 1985                                |
|   | 135–145   | Yakuji Nippo Ltd., 1987                         |
| Loss on drying                                  | $<1.0\%$  | Yakuji Nippo Ltd., 1987                         |
| Residue on ignition                             | $<1.0\%$  | Yakuji Nippo Ltd., 1987                         |

is a colorless waxy fat with a neutral odor consisting of a mixture of long-chain fatty esters and has pronounced hydrophobic properties (Labor L + S GMBH, 1993a;b). Its physical properties are similar or equivalent to those reported for Stearyl Heptanoate.

#### **Manufacture and Production**

Published data on the manufacture and production of Stearyl Heptanoate were not found.

#### **Analytical Methods**

Stearyl Heptanoate has been identified using infrared spectrophotometry (Yakuji Nippon Ltd., 1987).

#### **Ultraviolet Absorbance**

PCL-Solid does not absorb in the ultraviolet A (UVA) or UVB range (Dragoco, 1994).

#### **Impurities**

Stearyl Heptanoate contains <1.5 ppm chromium compounds, <0.4 ppm cadmium compounds, and <10.0 ppm lead compounds (as reported in accordance with Proposition 65) (Croda Inc., 1991). It also contains <10 ppm heavy metals and <1 ppm arsenic (Yakuji Nippo Ltd., 1987). Data as to organic impurities were not available.

#### **USE**

##### **Cosmetic**

The product formulation data submitted to the Food and Drug Administration (FDA) in 1994 stated that Stearyl Heptanoate was contained in a total of 121 cosmetic product formulations (Table 2). Stearyl Heptanoate was used in the formulation of eye makeup products, hair preparations, lipsticks, rouges, skin care preparations (excluding shaving preparations), and suntan preparations. The greatest reported use of Stearyl Heptanoate, 33 formulations, was in the formulation of body and hand skin care preparations.

Unpublished data submitted to CIR regarding PCL-Solid 2/066220 suggests that this mixture be used at the following concentrations: emulsions, 2–5%; stick formulations and lipsticks, 5–10%; lip balms, 5–25%; ointments, 3–5% (Dragoco, 1993); and cream perfumes, 10% (Labor L + S GMBH, 1993a;b).

##### **International**

Stearyl Heptanoate is listed in the Comprehensive Licensing Standards of Cosmetics by Category, Part II (Nikko Chemical Co., Ltd., 1992).

TABLE 2. Product formulation data for Stearyl Heptanoate (FDA, 1994)

| Product category  | Total no. of formulations in category | Total no. of formulations with Stearyl Heptanoate |
|---|---------------------------------------|---|
| Eye eyebrow pencil  | 100                                   | 1   |
| Eye liner   | 595                                   | 28  |
| Eye shadow  | 571                                   | 3   |
| Eye makeup remover  | 95                                    | 2   |
| Other eye makeup preparations                               | 132                                   | 2   |
| Hair sprays (aerosol fixatives)                             | 306                                   | 2   |
| Other hair preparations                                     | 376                                   | 2   |
| Blushers (all types)  | 279                                   | 1   |
| Lipstick  | 977                                   | 7   |
| Rouges  | 33                                    | 2   |
| Other makeup preparations                                   | 146                                   | 1   |
| Cleansing preparations                                      | 746                                   | 1   |
| Face and neck preparations (excluding shaving preparations) | 232                                   | 6   |
| Body and hand preparations (excluding shaving preparations) | 984                                   | 30  |
| Moisturizing preparations                                   | 839                                   | 7   |
| Night preparations  | 208                                   | 7   |
| Paste masks (mud packs)                                     | 282                                   | 3   |
| Skin fresheners   | 222                                   | 1   |
| Other skin care preparations                                | 790                                   | 14  |
| Suntan gels, creams, and liquids                            | 218                                   | 1   |
| 1994 Totals   |                                       | 121   |

### GENERAL BIOLOGY

Published data on Stearyl Heptanoate which would normally be summarized in the General Biology section were not found. Data from the safety assessment on Stearyl Alcohol (Elder, 1985) may be relevant.

Specifically, in a study investigating the effect of Stearyl Alcohol on the plasma membrane of cultured human lung fibroblasts, Stearyl Alcohol was inactive in inducing significant cellular damage.

### ANIMAL TOXICOLOGY

#### Acute Toxicity

##### Oral

Five male and five female fasted albino Sprague-Dawley rats were given a single oral dose of 16 ml/kg Stearyl Heptanoate by gavage (Inveresk Research International, 1977). A control group was dosed with 16 ml/kg water by gavage. Clinical observations were made for 14 days and the rats were then killed. Body weights were measured prior to dose administration, on day 7, and at study termination. No animals died during the study. The only observations were mild piloerection and slight diarrhea on day 1. Body weight gains were comparable to control values. The oral LD<sub>50</sub> of Stearyl Heptanoate for male and female albino Sprague-Dawley rats was >16 ml/kg.

Five male and five female fasted albino Sprague–Dawley rats were given a single oral dose of 5.0 g/kg of a cosmetic formulation containing 0.7% Stearyl Heptanoate in mineral oil USP by gavage (Hazleton Laboratories America, Inc., 1988a). (Dose volume was 10.0 ml/kg.) Clinical observations and mortality checks were made 1, 2.5, and 4 h after dosing and then once or twice daily, respectively, for 14 days. Body weights were measured prior to dose administration, on day 7, and at study termination. No animals died during the study and no clinical signs of toxicity were observed. The oral LD<sub>50</sub> of a formulation containing 0.7% Stearyl Heptanoate for male and female albino Sprague–Dawley rats was >5.0 g/kg.

### Subchronic Toxicity

#### *Percutaneous*

Published subchronic toxicity data on Stearyl Heptanoate were not found. Relevant data from the safety assessment on Stearyl Alcohol (Elder, 1985) were extracted and are summarized in this section.

No evidence of systemic toxicity was observed with a formulation containing 8.0% Stearyl Alcohol in a percutaneous study using rabbits.

### Dermal Irritation

Six albino rabbits, three per sex, were used to evaluate the primary dermal irritation potential of Stearyl Heptanoate (Inveresk Research International, 1977). The skin on the backs of the rabbits was clipped free of hair providing four application sites, two of which were abraded. Chromatography paper (1 sq. in.) wet with either 0.5 ml of the test material (undiluted) or sodium lauryl sulfate (a 10% solution in water) was applied to an intact and an abraded site on each rabbit for 24 h under occlusive patches. The test sites were rinsed after patch removal. The sites were scored immediately and 48 h after patch removal for erythema and edema according to the Federal Hazardous Substances Labeling Act (F.H.S.L.A.) scoring system (16CFR 1500.41).

The greatest average score for both erythema and edema produced by Stearyl Heptanoate was 1.00 for abraded skin after 24 h. The score for both erythema and edema for intact skin after 24 h was 0.83. The primary irritation score for Stearyl Heptanoate (determined by adding the erythema and edema scores for intact and abraded skin after 24 and 72 h and dividing each by 4) was 1.21/8. (The primary irritation score for Sodium Lauryl Sulfate was 3.51/8.) Stearyl Heptanoate was classified as mildly irritating.

### Sensitization

Albino Dunkin Hartley guinea pigs were used to determine the sensitization potential of a cosmetic formulation containing 1.5% Stearyl Heptanoate (Hazleton Laboratories America, Inc., 1987a). The animals were divided into a test group of 20 animals, 10 per sex, a negative control group of 10 animals, five per sex, and an irritation screen group of four animals, two per sex.

During the irritation screen, which was used to determine the animals' irritation

threshold for the material, the test article was applied undiluted or at concentrations of 25, 50, or 75% w/v in deionized water to the backs of the animals. Each animal received two concentrations of the test material. The test sites were examined 24 and 48 h after exposure. (The site was depilated 3 h before the 24-h reading using a commercial depilatory). It was determined from the results obtained during this screen that the test material was to be applied undiluted for the induction phase and as a 75% w/v suspension in deionized water for the challenge. The dose volume for all applications was 0.3 ml.

At induction, 0.3 ml of undiluted test material was applied to the shaved left shoulder of each animal using a Hilltop Chamber (25 mm diameter). The test site was wiped with a paper towel after 6 h of exposure. Each animal received one application per week for a total of three applications, and the application sites were examined and scored according to the Buehler scale 24 h after dosing and prior to the challenge application.

The challenge was performed 2 weeks after the third induction application. The challenge dose of 75% w/v test material in deionized water was applied to a previously unpatched site on the anterior right flank of the test group animals as well as to the previously untreated controls. The test sites were examined and scored 24 and 48 h after dose application. (The site was depilated 3 h before the 24-h reading using a commercial depilatory.)

General observations were made daily. Body weights were measured at study initiation, weekly throughout the study, and at study termination.

Five of the 20 animals of the test group and three of the 10 animals of the negative control group had faint dermal reactions (scores of 0.5) to the challenge application; reaction scores of the test animals were not greater than the reaction scores of the negative control animals. The incidence of a positive response (the number of animals having responses of  $\geq 1$  at either the 24 or 48 h challenge reading divided by the total number of animals tested) was 0 of 20 and 0 of 10 for the test and negative control groups, respectively. The severity of response (the sum of the test grades divided by the total number of animals tested) for animals of the test group was 0.1 after 24 h and 0.0 after 48 h. For animals of the negative control group, the severity was 0.2 after 24 h and 0.1 after 48 h. No significant clinical observations were made during the study. No significant differences in body weight gains were observed between the test and control groups.

### Ocular Irritation

Six albino rabbits, three per sex, were used to determine the ocular irritation potential of Stearyl Heptanoate (Inveresk Research International, 1977). A volume of 0.1 ml of undiluted test material was placed in the conjunctival sac of the right eye of each rabbit; the eyes were not rinsed. Irritation was scored according to the F.H.S.L.A. scoring system (16CFR 1500.42) after 1, 24, 48, and 72 h and after 7 days.

Ocular reactions were confined to the conjunctiva and persisted for several days. After 7 days, all eyes were normal except for very mild conjunctival erythema (0.5/3) in two animals. Stearyl Heptanoate was classified in Category 3 as an eye irritant.

Six New Zealand White rabbits (sex not specified) were used to determine the ocular irritation potential of a cosmetic formulation containing 1.5% Stearyl Heptanoate (Hazleton Laboratories America, Inc., 1987*b*). A volume of 0.1 ml of undiluted test material was placed on the everted lower lid of one eye of each rabbit; the eye was not rinsed. The other eye served as an untreated control. The eyes were examined for irritation using sodium fluorescein and scored according to the Draize scale (Draize, 1959) on days 1, 2, and 3. The maximum average score (MAS) (the greatest primary eye irritation score for any given observation period) and the primary eye irritation score (PII—total eye irritation score for all the animals divided by the total number of animals for each observation period) were both 0.0. No ocular irritation was observed for any of the animals at any observation period; therefore, a cosmetic formulation containing 1.5% Stearyl Heptanoate was not considered a primary eye irritant.

Six New Zealand White rabbits (sex not specified) were used to determine the ocular irritation potential of a cosmetic formulation containing 0.7% Stearyl Heptanoate (Hazleton Laboratories America, Inc., 1988*b*). A volume of 0.1 ml of an 80% w/v solution of the test material in mineral oil was placed on the everted lower lid of one eye of each rabbit; the eye was not rinsed. The other eye served as an untreated control. The eyes were examined for irritation and scored according to the Draize scale (Draize, 1959) at 1 h and on days 1, 2, and 3; sodium fluorescein was used to evaluate possible corneal injury at the first three readings. The MAS, which occurred on day 1, was 1.7 and the PIIs were 0.7 after 1 h, 1.7 on day 1, 0.3 on day 2, and 0.0 on day 3. No corneal or iridal irritation was observed in any of the animals. A cosmetic formulation containing 0.7% Stearyl Heptanoate was not considered a primary eye irritant.

#### Comedogenicity

Six male New Zealand White rabbits were used to examine the comedogenic potential of a cosmetic formulation containing 1.5% Stearyl Heptanoate (Hilltop Biolabs, Inc., 1987*a*). The material was applied undiluted to the inner surface of the basal portion of the right ear of each rabbit using the tip of a 2.5 ml syringe. An empty syringe rubbed across the left ear served as the negative control. Three rabbits were treated 5 days/week for 2 weeks while the other three rabbits were treated 5 days/week for 4 weeks. All ears were scored for comedone formation (on a scale of 0 to 4) after every fifth application and prior to study termination. The animals were killed at the end of the study and the ears were removed and processed so that the epidermal tissue could be examined microscopically.

During the study, the following irritative effects were noted in the right ear of one or more animals: erythema; small scratches; slight to extreme desquamation; slight thickening; red or yellow appearance in color; brown spots; and reddish-brown discoloration. No significant irritation was observed.

For animals dosed for 2 weeks, the greatest average in-life comedone score was 3.33 on day 5, with one animal having a score of 4 (severe, confluent involvement) and the other two having scores of 3 [moderate (extensive) comedone formations]. The average scores on days 12 and 15 were 2.67 and 2.0, respectively. The av-

erage scores for the control ear were 0, 0.67, and 0.67 on days 5, 12, and 15, respectively.

For animals dosed for 4 weeks, the greatest average in-life comedone score was 2.33 on day 5, with one animal having a score of 3 and the other two having scores of 2 [mild (several) comedone formations]. The average score was 2.0 on days 12, 15, 22, and 26 and 1.33 on day 29 [a score of 1 corresponded to trace (few) comedone formations]. The average control scores varied from 0 to 1.0 during the 4 weeks of dosing. The average comedone scores in the processed tissues were 1.67 and 1.0 for the animals treated 2 and 4 weeks, respectively; the average control score was 0 for both groups. The authors concluded that a cosmetic formulation containing 1.5% Stearyl Heptanoate produced slight to moderate comedogenicity in rabbit ears.

### Reproductive and Developmental Toxicity

Published teratogenic/reproductive data on Stearyl Heptanoate were not found. The one relevant study on the teratogenicity of heptanoic acid concluded that heptanoic acid had teratogenic potential in vitro but, using structure-metabolism relation analysis, is unlikely to have teratogenic potential in vivo because of its susceptibility to  $\beta$ -oxidation (Di Carlo, 1990).

### MUTAGENICITY

The mutagenic potential of PCL-Solid 2/066220 was examined using the Ames *Salmonella*/microsome plate incorporation assay (Labor L + S GMBH, 1993a). PCL-Solid 2/066220 in dimethyl sulfoxide (DMSO), 8.0–5,000  $\mu\text{g}/\text{plate}$  (concentration range determined using a preliminary study), was assayed with and without metabolic activation using *Salmonella* strains TA100, TA1535, TA98, TA1538, and TA1537. Positive and negative controls were used. Without metabolic activation, the positive controls were Na azide for strains TA100 and TA1535; 2-nitrofluorene for strains TA98 and TA1538; and 9-aminoacridine for strain TA1537. With metabolic activation, 2-aminoanthracene was the positive control for all the *Salmonella* tester strains. The vehicle served as the negative control for all strains with and without metabolic activation. Two trials were performed. PCL-Solid 2/066220, 8.0–5,000.0  $\mu\text{g}/\text{plate}$ , did not induce base pair or frameshift mutations with or without metabolic activation.

The mutagenic potential of PCL-Solid 2/066220 was also examined using an in vivo micronucleus test (Labor L + S GMBH, 1993b). NMRI mice, five males and five females per group, were given a single oral dose of 500, 1,500, or 5,000 mg/kg PCL-Solid 2/066220 in corn oil at a volume of 10 ml/kg. Two negative control groups and a positive control group dosed with vehicle and cyclophosphamide, respectively, were used. Animals of the test and control groups were killed 24 h after dosing; mice of an additional group dosed with 5,000 mg/kg PCL-Solid 2/066220 were killed 48 h after dosing.

No clinical signs were observed for any of the test animals following dose administration. After 24 or 48 h, the number of polychromatic erythrocytes with or without micronuclei, the number of normochromatic erythrocytes, and the



ratio of poly- to normochromatic erythrocytes observed for the test animals did not differ significantly from historical or negative control values. PCL-Solid 2/066220 did not have a clastogenic effect.

### CARCINOGENICITY

Published carcinogenicity data for Stearyl Heptanoate were not found. Data from the safety assessment on Stearyl Alcohol (Elder, 1985), however, indicated that Stearyl Alcohol did not promote tumor formation in female Swiss mice when initiated with 7,12-dimethylbenz[*a*]anthracene.

### CLINICAL ASSESSMENT OF SAFETY

#### Irritation and Sensitization

In a repeated insult patch test (RIPT) using 50 subjects, Stearyl Heptanoate had zero potential for irritation and sensitization (Croda Inc., 1991).

A modified Draize skin sensitization study was completed using 198 subjects (53 men and 145 women) who were free of any active skin disease to determine the dermal sensitization potential of a cosmetic formulation containing 0.7% Stearyl Heptanoate (CTFA, 1987*a*). The test material was applied as a 75% w/v in mineral oil solution to the upper arm or back of the subjects using an occlusive patch. During the 3-week induction period, the patches were applied three times weekly for 48–72 h. Approximately 2 weeks after the induction phase, challenge patches were applied to a previously unpatched site. The patches were removed 72 h after application and the sites were scored (on a scale of 0 to 4) 96 h after application. No reactions were observed following the challenge application and, at any given reading, an equivocal reaction in four or less subjects was the only reaction observed during induction. A 75% w/v solution of a formulation containing 0.7% Stearyl Heptanoate did not produce a sensitization response in any of the subjects. Also, it did not induce or elicit allergic contact dermatitis.

A Draize study, for which it is assumed the same method as above (CTFA, 1987*a*) was followed, was completed using 194 subjects (56 men and 138 women) to determine the dermal sensitization potential of a cosmetic formulation containing 1.5% Stearyl Heptanoate (CTFA, 1987*b*). The formulation was applied undiluted. During induction, equivocal reactions in a few subjects were observed. Following the challenge application, a score of 1 (erythema) was observed for two subjects after 72 h and no reactions were observed after 96 h. A formulation containing 1.5% Stearyl Heptanoate was not a sensitizer.

A human RIPT was completed using 202 subjects (26 men and 176 women) to determine the irritation and sensitization potential of a cosmetic formulation containing 1.5% Stearyl Heptanoate (Concordia Research Labs, Inc., 1990*a*). (It was not stated whether the test material was diluted.) The test material did not produce any clinically significant dermal reactions. Some scattered minor reactions were observed during the induction phase. A score of 3+/5+ was observed at induction observation periods 2, 3, and 4 for one subject and at observation period 6 for another; all remaining observed reactions were scores of 1+/5+. During the

challenge, a score of 2+/5+ after 48 h and a score of 3+/5+ after 96 h was observed for one subject; a score of 1+/5+ was observed for two subjects after 48 h and for one subject after 96 h. The investigators concluded that the irritation and sensitization potential of a formulation containing 1.5% Stearyl Heptanoate was "very low, if existent at all".

A modified Draize RIPT was completed using 156 subjects (27 men and 129 women) to determine the irritation and sensitization potential of a cosmetic formulation containing 1.5% Stearyl Heptanoate (Concordia Research Labs, Inc., 1990b). (It was not stated whether the test material was diluted.) The test material did not produce any clinically significant dermal reactions. Some scattered minor reactions were observed during the induction phase (scores of 1+/5+). No reactions to the challenge application were noted. The investigators concluded that the irritation and sensitization potential of a formulation containing 1.5% Stearyl Heptanoate was "very low, if existent at all".

### Comedogenicity

An assay was completed using 12 female subjects based on the method described by Mills and Kligman (1982) to determine the comedogenic potential of a cosmetic formulation containing 1.5% Stearyl Heptanoate (Hilltop Biolabs, Inc., 1987b). (Subjects that had a history of acne and a predisposition towards the formation of comedones were selected.) The test material was applied under occlusive patches to a 4 cm<sup>2</sup> area of the back, above the scapulae, 3 days/week for 4 weeks, providing 28 days of continual exposure. (It was not stated whether the test material was diluted.) An adjacent 4 cm<sup>2</sup> site served as the untreated control site. After 4 weeks, the sites were sampled by the cyanoacrylate follicular biopsy technique and examined under a stereomicroscope. Comedogenic potential was scored on a scale of 0 to 3; an average score  $\geq 1$  was considered comedogenic. The average of the difference in the scores of the treated and untreated sites for the 12 subjects was used to evaluate the comedogenic potential of the test material. A formulation containing 1.5% Stearyl Heptanoate was not comedogenic, with an average difference in scores (treated – untreated) of 0.12 (all scores were 0, with the exception of one score of 0.5 and one of 1.0).

### SUMMARY

Stearyl Heptanoate is the ester of stearyl alcohol and heptanoic acid. It is an off-white waxy solid, and, as a 10% solution, is soluble in ethanol, mineral oil, corn oil, oleyl alcohol, and castor oil. However, it is not soluble in water. Stearyl Heptanoate has been identified using infrared spectrophotometry.

A commercial product, tradename PCL-Solid 2/066220, is a mixture containing at least 50% Stearyl Heptanoate. It is a colorless waxy fat that has pronounced hydrophobic properties with physical properties that are similar or equivalent to those of Stearyl Heptanoate. PCL-Solid does not absorb in the UVA or UVB range.

Stearyl Heptanoate functions as a skin conditioning agent–occlusive in cosmet-

ics. In 1994, Stearyl Heptanoate was reported to be used in 121 cosmetic formulations of various product categories.

Recommended concentration of use values for PCL-Solid 2/066220 are: emulsions, 2–5%; stick formulations and lipsticks, 5–10%; lip balms, 5–25%; ointments, 3–5%; and cream perfumes, 10%.

A formulation containing 0.7% Stearyl Heptanoate had an oral LD<sub>50</sub> of >5 g/kg for male and female Sprague–Dawley rats and was practically nontoxic according to the terminology of Hodge and Sterner (1949). In another study, the oral LD<sub>50</sub> of Stearyl Heptanoate for male and female albino Sprague–Dawley rats was >16 ml/kg.

Stearyl Heptanoate (undiluted) was mildly irritating when applied to the backs of rabbits. A cosmetic formulation containing 1.5% Stearyl Heptanoate was not a sensitizer using guinea pigs, but it did produce slight to moderate comedogenicity in rabbit ears.

Stearyl Heptanoate (undiluted) was a Category 3 ocular irritant (according to the F.H.S.L.A. scoring system) using rabbits. Formulations containing 1.5% or 0.7% Stearyl Heptanoate were not primary ocular irritants.

PCL-Solid neither induced base pair or frameshift mutations, with or without metabolic activation, in an Ames *Salmonella*/microsome plate incorporation assay, nor had a clastogenic effect in an in vivo micronucleus test.

In modified Draize tests using 198 and 194 subjects to evaluate formulations containing 0.7% and 1.5% Stearyl Heptanoate, respectively, the formulations were not sensitizers. A human RIPT using 202 subjects and a modified Draize RIPT using 156 subjects were performed to evaluate the irritation and sensitization potential of formulations containing 1.5% Stearyl Heptanoate; the irritation sensitization potential of the formulations was very low, if existent at all. A cosmetic formulation containing 1.5% Stearyl Heptanoate was not comedogenic for humans.

## DISCUSSION

The safety of Stearyl Heptanoate for use in cosmetic formulations was considered by the Expert Panel utilizing data on the mixture PCL Solid 2/066220 in its review. These data are relevant to this evaluation because the concentration of Stearyl Heptanoate in this mixture is >50%.

Additionally, the Expert Panel recognizes that although animal irritation testing was done at 100%, sensitization testing was performed using a maximum concentration of only 1.5% Stearyl Heptanoate, and Stearyl Heptanoate is used at greater concentrations in formulation. However, all available data suggest that it would not be a sensitizer, even at higher concentrations. Only mild reactions were seen in ocular irritation testing with undiluted Stearyl Heptanoate, and concentrations up to 1.5% were not primary ocular irritants. The Expert Panel is of the opinion that Stearyl Heptanoate, as used in cosmetic formulations, would not produce significant ocular irritation.

## CONCLUSION

On the basis of the animal and clinical data presented in this report, the CIR Expert Panel concludes that Stearyl Heptanoate is safe for use as a cosmetic ingredient in the present practice of use.

**Acknowledgment:** This report was prepared by Monice M. Fiume, Scientific Analyst/Report Management Coordinator.

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