AMENDED FINAL REPORT ON THE SAFETY ASSESSMENT OF PENTAERYTHRITYL ROSINATE[1]

Pentaterythrityl Rosinate (previously called Pentaerythritol Rosinate) is the ester of rosin acids with the polyol pentaerythritol. It is used as a skin conditioning agent—emollient and viscosity increasing agent–nonaqueous in a few cosmetic formulations. In a previous safety assessment, it was concluded that the available data were insufficient to support the safety of this ingredient in cosmetic products. Additional data needed included: concentration of use, source and method of manufacture, chemistry (ultraviolet [UV] spectral analysis, pH, and impurities), ocular irritation, human dermal irritation and sensitization, and photosensitization (only if Pentaerythritol Rosinate absorbs UVA or UVB light). It was also noted that the carcinogenic potential of this ingredient was still of concern because of the low concentration tested in the available carcinogenicity study. Additional data were received. This ingredient is produced by the fractional distillation of crude tall oil to form rosin, which is then esterified with monopentaerythritol. It is typically used at concentrations of 0.5–10%. It does not significantly absorb in the UVA or UVB portion of the spectrum. Formulations with 10% Pentaerythrityl Rosinate produced only minimal ocular irritation. Likewise tests of formulations with the ingredient at concentations of 7–9.2% resulted in minimal dermal irritation. The ingredient was nonsensitizing in animal maximization tests. Clinical tests of formulations with the ingredient at concentrations of 7–9.6% resulted in neither irritation nor sensitization. No data, however, were provided on possible impurities. Absent information on the actual chemical structure, the lack of information on impurities was considered significant. On further review, a single carcinogenicity study with negative results reported in the earlier safety assessment was considered inadequate. The absence of genotoxicity data was also considered significant. The lack of impurity and chemical structure information also raised a concern about the need for reproductive and developmental toxicity data. On the basis of this further review, it was concluded that the available data are still insufficient to support the safety of this ingredient in cosmetic products. Additional data needed include: (1) two genotoxicity assays, at least one in a mammalian system; if positive, then a 2-year dermal carcinogenicity study using National Toxicology Program (NTP) methods is needed; (2) dermal absorption; if significantly absorbed, then both a 28-day dermal toxicity study and a reproductive and developmental toxicity study may be needed; and (3) chemical properties, including structure and impurities.

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This report is an amendment to the previous safety assessment on Pentaerythritol Rosinate (now known as Pentaerythrityl Rosinate). Pentaerythrityl Rosinate is the ester of rosin acids derived from rosin (q.v.) with the polyol pentaerythritol. It is used as a skin-conditioning agent—emollient and viscosity increasing agent–nonaqueous in cosmetic formulations. In the Final Report on the Safety Assessment of Pentaerythritol Rosinate (Andersen 1994), the Cosmetic Ingredient Review (CIR) Expert Panel concluded that:

> The data available on Pentaerythritol Rosinate are insufficient to support the safety of this ingredient as used in cosmetic products. The following data are necessary to make a safety assessment: (a) concentration of use, (b) source and method of manufacture, (c) chemistry (ultraviolet [UV] spectral analysis, pH, and impurities), (d) ocular irritation, (e) human dermal irritation and sensitization, and (f) photosensitization (only if Pentaerythritol Rosinate absorbs UVA or UVB light).

Based on its evaluation of additional data, and reconsideration of previously available data, the CIR Expert Panel has revised its conclusion.

CHEMISTRY

Definition and Structure

Pentaerythrityl Rosinate (CAS No. 8050-26-8) is the ester of rosin acids derived from rosin (q.v.) with the polyol pentaerythritol (Wenninger and McEwen 1997). The chemical structure for Pentaerythrityl Rosinate is not available; however, the chemical structure for the polyol Pentaerythritol is shown in Figure 1 (Budavari 1989; STN International 1995). Other names for Pentaerythrityl Rosinate are pentaerythritol rosinate (Chemline 1995; Wenninger and McEwen 1997); pentaerythritol ester of rosin; rosin, pentaerythritol ester; rosin, pentaerythrityl resin; and rosin, pentaerythritol polymer (Chemline 1995).

Chemical and Physical Properties

The drop-softening point for the pentaerythritol ester of disproportionated rosin is 92–98°C. The color (determined using a 1963 Gardner Color

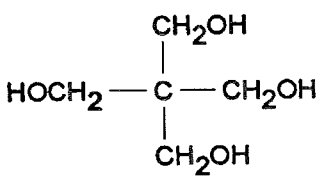

Figure 1. Chemical formula for pentaerythritol.

Dish) has a maximum of 7+, and the acid number (representing unreacted rosin) maximum is 14. The stabilized (glycerol ester) version of this compound has an acid number maximum of 10, softening point of 80–86°C, and color maximum of 8. The flash point is typically >400°F, and the specific gravity is 1.06 (CTFA 1995a).

Pentaerythrityl Rosinate as used in chewing gum bases and wood preservatives has an acid number of 6–16, a drop-softening point of 109–116°C, and a color of M or paler as specified in the Code of Federal Regulations (21 CFR 172.615 and 21 CFR 178.3870).

Method of Manufacture

The particular rosin used in the manufacture of Pentaerythrityl Rosinate (disproportionated rosin) is obtained by the fractional distillation of crude tall oil, a by-product of the Kraft paper pulping process. The rosin is esterified with commercially available monopentaerythritol to a maximum residual acid value of 14. The finished resin is typically flaked or pastillized for sale in bags (CTFA 1995a).

Impurities

Principal components (detected by gas permeation chromatography and mass spectrometry) of the finished product are the tetra-ester (46.3%), tri-ester (44.6%), and unreacted rosin (6.3%) (CTFA 1995a).

Ultraviolet Absorbance

A sample solution of 1.891 g of pentaerythrityl rosinate diluted to 1 liter in methanol was scanned (by USP XXI method) using a UV-Vis spectrophotometer from 400 to 300 nm at 25°C. Absorptivities at 360 (UVA) and 310 nm (UVB) were 0.02 and 0.2, respectively. A typical absorbtivity for a sunscreen scanned under the same conditions would have been 65.0 (CTFA 1995a; b).

USE

Cosmetic

Pentaerythrityl Rosinate is used as a skin conditioning agent—emollient and as a viscosity increasing agent–nonaqueous in cosmetic product formulations (Wenninger and McEwen 1997). Product formulation data (Table 1) submitted to the Food and Drug Administration (FDA) in 1996 reported that Pentaerythrityl Rosinate was used in a total of seven cosmetic formulations (FDA 1996). Concentration of use data submitted

Table 1. Product formulation data

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Eye shadow	588	2
Mascara	218	1
Foundations	355	1
Makeup bases	154	1
Nail polish and enamel	113	2
1996 total		**7**

Source. FDA, 1996.

to the FDA in 1984 stated that Pentaerythrityl Rosinate was used at concentrations up to 10% in mascaras (FDA 1984). The use concentration values shown in Table 2 have since been reported by one cosmetic company (CTFA 1995b).

Noncosmetic

Pentaerythrityl Rosinate is an indirect food additive that has been listed in the Code of Federal Regulations for use as a component of adhesives (21 CFR 175.105), resinous and polymeric coatings (21 CFR 175.300), paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170), and defoaming agents used in the manufacture of paper and paperboard (21 CFR 176.210). Pentaerythrityl Rosinate is also a direct food additive (plasticizing material and softener) in chewing gum bases (21 CFR 172.615), and an indirect food additive in animal glues (21 CFR 178.3120) and wood preservatives (21 CFR 178.3870) for articles used to package, store, and/or transport raw agricultural products.

Table 2. Concentration of use of Pentaerythrityl Rosinate

Cosmetic product	% Pentaerythrityl rosinate
Eyeliners	7.0
Eye shadows	0.75
Mascaras	9.6
Hair coloring	2.6
Body foundation	0.5

Source. CTFA, 1996.

ANIMAL TOXICOLOGY

Ocular Irritation

Pentaerythrityl Rosinate was evaluated for its potential to produce ocular irritation. In one study, 10% Pentaerythrityl Rosinate in mineral oil was instilled into the conjunctival sac of three rabbits in a Draize test (volume not given in this or the following tests). The eyes were not rinsed after applications, and no anesthesia was used during the study. The cornea, iris, and conjunctiva were examined at 1, 2, and 3 days after instillation. At day 1, all three rabbits had conjunctival scores of 2/20. The irritation persisted until day 2 in one of the three rabbits. No other signs of irritation were noted. The total and average scores for the test were 2/110 for day 1, 1/110 for day 2, and 0 for day 3. Ocular irritation potential for 10% Pentaerythrityl Rosinate was minimal by the Draize classification scale for ocular irritation. Mascara containing 9.2% Pentaerythrityl Rosinate was instilled three times into the conjunctival sac of six rabbits in a second Draize eye irritation test. The eyes were unrinsed and no topical aesthesia was administered. Ocular examinations were performed at days 1–4 postdose. Two rabbits had conjunctival scores of 2/20 on day 1, and one rabbit had a score of 2/20 on day 3. Average and total scores were 1 for both days 1 and 3, and 0 for days 2 and 4, indicating minimal ocular irritation. In a third Draize eye irritation test, undiluted eyeliner containing 7.0% Pentaerythrityl Rosinate was instilled into the conjunctival sac of six rabbits. Reactions were evaluated at 1, 2, 3, and 4 days after dosing. On day 3, two rabbits had conjunctival scores of 2/20, and no other irritation was detected. The average and total scores were both 1, and the ocular irritation potential of the test formulation was minimal (CTFA 1995b).

Dermal Irritation

Pentaerythrityl Rosinate diluted to a concentration of 25% in mineral oil was tested on the skin of nine rabbits (strain not given) in a single insult occlusive patch test. Application sites were evaluated at 2 hours and 24 hours postdosing and reactions were graded with a maximum primary irritation index (PII) of 8. The PII for the group was 0.78, and skin irritation potential was minimal. A mascara containing 9.2% Pentaerythrityl Rosinate was applied to the skin of nine rabbits in a similar single insult occlusive patch test. At 2 hours and 24 hours postdosing, all nine rabbits had PII scores of 4/8 to give a total of 4.0 for the group. Skin irritation potential was considered moderate. In a third primary irritation test, eight rabbits received occlusive patches containing undiluted eyeliner (7.0% Pentaerythrityl Rosinate). All rabbits had PIIs of 4/8 at both 2 hours and 24 hours after application of the patch. The group

PII was therefore 4.0, and skin irritation potential was judged moderate (CTFA 1995b).

Dermal Sensitization

Pentaerythrityl Rosinate did not have a discernible potential for allergic skin sensitization when tested using a Magnusson-Kligman maximization procedure. Seventy female albino Hartley guinea pigs (each weighing 250–300 g) were housed in groups of five in suspended, wire-floored cages. Temperature and humidity were controlled, and feed and water were available ad libitum. After a 1-week acclimation period, the guinea pigs were randomly assigned to five groups. Group I included 30 guinea pigs, and the remaining four groups each had 10. Group I was further divided into two groups of 15 animals each. During the induction phase, the backs of Groups II–V guinea pigs were shaved, and Group I guinea pigs were not. Test animals of Groups II–IV received 0.5 ml intradermal injections into three sites on the left upper back and three sites on the right upper back. For Group II, the first injection was 50% aqueous Freund's adjuvant, the second was 5.0% Pentaerythrityl Rosinate in propylene glycol, and the third was 5.0% Pentaerythrityl Rosinate in 50% Freund's adjuvant. The same injections were made to Group V guinea pigs, but turpentine was used instead of Pentaerythrityl Rosinate and served as the positive control. Group I guinea pigs were untreated and served as the negative control. The remaining groups received other test materials. In the booster phase, topical application of the test material was made one week after the induction injections. Group I received no booster and Group II and Group V were dosed with 15% Pentaerythrityl Rosinate and 25% turpentine, respectively, in petrolatum. The test material at doses of 0.5 ml was applied to a 1″ × 1″ Webril dressing pad over the appropriate induction injection site. The booster was under occlusive patches for 48 hours using Saran Wrap, Elastoplast Adhesive, and masking tape. Untreated control guinea pigs of Group I were not wrapped. Two weeks after the end of treatment, the guinea pigs were challenged with 0.5 ml of their respective test materials on previously untreated sites located on the left or right flank. Half of Group I was treated with 15% Pentaerythrityl Rosinate in petrolatum on the left flank, and the remaining 15 guinea pigs were treated with 2% turpentine in petrolatum on the right flank. Group II had 15% Pentaerythrityl Rosinate in petrolatum applied to the left flank, and Group V was treated with 2% turpentine in petrolatum on the left flank. Test materials were applied to occlusive Webril patches shortly before application to the skin for 24 hours. The sites were graded for erythema 24 hours and 48 hours after patch removal. Two guinea pigs from the untreated control group,

and five from Group II died during the study. The causes of death were infections by microbial agents commonly found in the respiratory flora, and were not related to the application of the test products. In the surviving animals, one untreated control animal has a (±) reaction (barely perceptible erythema). No signs of allergic skin sensitization were detected in Group II, and the positive control group had mild to moderate reactions (CTFA 1995b).

CLINICAL ASSESSMENT OF SAFETY

Dermal Sensitization

A repeated insult patch test (RIPT) was utilized to evaluate the contact allergenicity potential of an eyeliner containing 7.0% Pentaerythrityl Rosinate. Fifty adult male and female volunteers were screened for admission to the study; two withdrew for reasons unrelated to the test. A dose of 0.1 ml of the test material was added to 20 × 20 mm Webril patch affixed to the center of a 40 × 40 mm adhesive bandage shortly before application to the test site. The occlusive patches were secured with Scanpor tape to the upper back of each panelist. Five were placed on the right side, and five to the left side, adjacent to the mid-line, for 24 hours every Monday, Wednesday, and Friday for three consecutive weeks. Application sites remained the same unless the reactions observed were severe, at which point the sites were changed. Three weeks after the completion of the induction phase, a single patch of the test material was applied to a previously untreated site, and removed 24 hours later. The test sites were scored at patch removal and after an additional 24 hours and 48 hours. One subject had (±) reactions (barely perceptible erythema) on the first and third induction applications, and a reaction of 1 (mild erythema covering most of the contact site) on the second application. No other reactions were detected during the induction or challenge phases. The eyeliner tested did not have any potential for inducing allergic sensitization (CTFA 1995b).

In a second RIPT, also submitted by CTFA (1995b), 78 panelists were tested with mascara containing 9.6% Pentaerythrityl Rosinate. One subject withdrew from the test for reasons unrelated to the test. After the above procedure was performed, no erythematous reactions were observed. Investigators concluded that "the product possessed a negligible potential for producing allergic contact dermatitis under foreseeable conditions of usage."

A waterproof mascara containing 9.21% Pentaerythrityl Rosinate was also tested. Eighteen of the 112 panelists enrolled in the study were removed from the experiment due to excessive absences unrelated to the test materials. Patches similar to the ones described above were used to

apply the ~0.2 g mascara (after product volatiles had evaporated) to the left and right sides of the back, adjacent to the midline. Patches were applied three times per week for three consecutive weeks and removed after 24 hours. Two weeks after the ninth induction application, one set of patches was applied for 24 hours to the original site and one set to previously untreated skin. Challenge sites were then evaluated 48 hours and 96 hours after application. Positive reactions are given in Table 3 (CTFA 1995b).

Table 3. Positive induction phase results of RIPT—mascara

Subject	Application no.	Results[a]
1	1–3	Definite erythema & D; adjacent site also patched due to reaction
	2–3	Adjacent site had no reaction
2	2	Vesicular eruption; adjacent site patched
	3	Absent
	4	Definite erythema and edema & D; no reaction at new site
	5	Definite erythema & D at both sites
	6–7	Barely perceptible erythema & D at original site with adjacent patch omitted
	8–9	All patches omitted for 8–9 due to previous strong reactions
3	3	Definite erythema
	4–5	Definite erythema & A
4	4–9	Barely perceptible erythema & A
5	8	Barely perceptible erythema & A
	9	Absent
6	2	Definite erythema & C; adjacent site patched
	3	Definite erythema & C at original site; no reaction at adjacent site
	4–6	Barely perceptible erythema & C at original site; no reaction at adjacent site
7	4	Barely perceptible erythema
	5	Absent
	6–9	Barely perceptible erythema & B
8	5	Absent
	7	Barely perceptible erythema
	Makeup	Definite erythema & D

[a]Effects on superficial layers of skin: A, Marked glazing; B, Glazing with peeling and cracking; C, Glazing with fissure; D, Film of dried serous exudate covering all or portions of the patch site.

Source. CTFA, 1995b.

Table 4. Induction results for RIPT—eyeshadow

	Number of subjects Induction application no.								
Reactions	1	2	3	4	5	6	7	8	9
Mild reaction (weak but definite erythema with weak superficial skin responses such as glazing, cracking, and peeling)	1	7	11(1[a])	5	7	2	0	3	2
Definite papular response	1	1	0	0	0	0	0	0	0

[a]Due to the severity of the response, a second patch was applied adjacent to the first in one subject.

Source. CTFA, 1995b.

A concentration of 0.5% pentaerythrityl rosinate in a body foundation was tested in the same manner and was minimally irritating. Of the subjects, 110 of 127 completed the study; those who were removed were repeatedly absent for reasons unrelated to the test material. Ten of the remaining subjects had barely perceptible erythema during at least one of nine induction applications: two after the first application, one after the third, three after the sixth, one following the seventh, and the remaining three at the eighth application. No panelist had erythema on more than one day, and none reacted to the challenge application. Investigators concluded that the test formulation was a nonprimary sensitizer and nonprimary irritant (CTFA 1995b).

After the volatiles in the formulation had been evaporated, an eyeshadow cream containing 1.0% Pentaerythrityl Rosinate was tested in a RIPT. A panel of 105 individuals completed the study, and 22 had erythema at some point during the induction phase. None reacted to the challenge dose. Reactions are described in Table 4 (CTFA 1995b).

Four-Day Cumulative Irritation

A cream eyeshadow base (9.2% Pentaerythrityl Rosinate) was evaluated in a 4-day minicumulative irritation patch assay for potential to cause irritation from repetitive exaggerated exposure. Twenty subjects had occlusive patches containing ~0.2 cc of the test material placed on the upper back. The patches were removed after 24 hours and new patches were applied to the same site daily for four consecutive days. Five hours after removal of the fourth patch, test sites were graded for irritation. Of the panelists, 15 of 20 did not react to the test material, and the remaining five subjects had barely perceptible erythema (±). The PII for the test

group was 0.13 (essentially nonirritating), whereas the positive control group (control not given) PII was 0.95 (moderately irritating). The formulation tested in the assay "exhibited acceptable irritation results." A cream eyeshadow containing 1.0% Pentaerythrityl Rosinate was tested using the same procedure and was essentially nonirritating. Fourteen of 16 panelists did not demonstrate signs of skin irritation, and 2 of 16 had a (±) reaction (CTFA 1995b).

SUMMARY

Pentaerythrityl Rosinate, then called Pentaerythritol Rosinate, was previously reviewed by the CIR Expert Panel in 1993. The final safety assessment was published (Andersen 1994) with the conclusion that the available data were insufficient to assess the safety. The data needed in order to complete the safety assessment included:

1. concentration of use;
2. source and method of manufacture;
3. chemistry (UV spectral analysis, pH, and impurities);
4. ocular irritation;
5. human dermal irritation and sensitization; and
6. photosensitization (only if the ingredient absorbs UVA or UVB light).

It was also noted in that report that the carcinogenic potential of Pentaerythritol Rosinate was still of concern because of the low concentration tested (0.050%) in the carcinogenicity study. Data addressing each of these needs were received in 1995. These data are summarized below.

Pentaerythrityl Rosinate is the ester of rosin acids derived from rosin with the polyol pentaerythritol. Pentaerythrityl Rosinate is produced by the fractional distillation of crude tall oil to form rosin, which is then esterified with mono-pentaerythritol. Pentaerythrityl Rosinate functions as a skin conditioning agent—emollient and nonaqueous viscosity-increasing agent. In 1996, Pentaerythrityl Rosinate was reported to be used in seven cosmetic formulations. The ingredient is typically used at concentrations from 0.5–10%. No significant absorbance in the UVA or UVB region of the spectrum was found. Mascara containing 10% Pentaerythrityl Rosinate caused minimal irritation in ocular toxicity studies using rabbits. Pentaerythrityl Rosinate at a concentration of 25% produced minimal irritation to the skin of rabbits in a single insult patch test. Eyeliner and mascara formulations containing 7–9.2% Pentaerythrityl Rosinate produced moderate dermal irritation in rabbits. Pentaerythrityl Rosinate at a concentration of 15% was nonsensitizing to the skin of guinea pigs in a Magnusson-Kligman maximization test. Formulations containing 7–9.6% Pentaerythrityl Rosinate did not

induce sensitization reactions or dermal irritation in human repeated insult patch tests.

DISCUSSION

The CIR Expert Panel recognized that the data received addressed most of the data elements previously considered necessary in order to complete the safety assessment. Not included in the recent information provided by industry was information on possible impurities. Although not specifically requested in the earlier report, the absence of the actual chemical structure of Pentaerythrityl Rosinate was also a concern. These missing data led the Panel to reconsider the question of carcinogenic potential. The available data had suggested that there was no evidence of carcinogenicity during chronic oral studies with rats and dogs fed Pentaerythrityl Rosinate at 0.05% of their diet for 2 years (Industrial Bio-Test Laboratories, Inc. 1962a; b). Upon further review, these carcinogenicity data were not considered adequate. The Panel noted that the availability of carcinogenicity data had overshadowed the absence of any genotoxicity data. Such data should be developed before any investment is made in a further 2-year carcinogenesis study using NTP methods. In addition, the Expert Panel now considers the absence of reproductive or developmental toxicity data, in light of the missing impurities data and chemical structure information, to be a deficiency.

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." Accordingly, the Expert Panel has reached an "insufficient data" tentative conclusion. This tentative conclusion was announced on June 4, 1996. A period of 90 days is provided during which interested parties are invited to comment, provide information, undertake work adequate and appropriate to resolve the questions, or request an oral hearing before the Expert Panel. The data necessary to complete a safety assessment are (1) two genotoxicity assays, at least one in a mammalian system; if positive, then a 2-year dermal carcinogenicity study using NTP methods is needed; (2) dermal absorption; if significantly absorbed, then both a 28-day dermal toxicity study and reproductive and developmental toxicity study may be needed; and (3) chemical properties, including structure and impurities.

CONCLUSION

The CIR Expert Panel concludes that the data available on Pentaerythrityl Rosinate are insufficient to support the safety of this ingredient as used in cosmetic products.

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