Safety Assessment of Phytantriol as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	November 10, 2022
Panel Meeting Date:	December 6-7, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen.; Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Regina Tucker, M.S., Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651
cirinfo@cir-safety.org

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Regina Tucker, MS
Scientific Analyst/Writer, CIR
Date: November 10, 2022
Subject: Re-Review of the Safety Assessment of Phytantriol

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review on the safety of Phytantriol in 2007 identified as (*originalreport_Phytantriol_122022* in the pdf), with the conclusion that Phytantriol is safe as a cosmetic ingredient in the practices of use and concentration as described in that safety assessment.

Because it has been at least 15 years since the final amended report was published, in accordance with CIR Procedures, the Panel should consider whether the safety assessment of Phytantriol should be reopened. An exhaustive search of the world's literature was performed for studies dated 2000 forward. An historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed herein *(newdata_Phytantriol_122022).*

A case study of a 44-year-old woman with no past medical history and no exposure to known irritants presented with an acute eczematous skin reaction on the face after utilizing a face cream with Phytantriol. Patch testing revealed the source of the contact allergy was Phytantriol at concentration 0.02-0.5%.

Also included for your review are current and historical use data on Phytantriol (*usetable_Phytantriol_122022)*. The frequency of use has decreased since the original report was issued, from 94 formulations (as reported in the 2002 final report) to 82 formulations in 2022. The maximum concentration of use reported in response to a 2022 survey is 0.54%. The maximum use concentration reported by industry in 2003 was 0.1%. However, it should be noted that personal communication submitted to CIR in 2004 indicated that the expected use concentration in products under development was 3%; accordingly, the conclusion that was reached in the original report considered use up to 3%.

If upon review of the new information the Panel determines that a re-review is warranted, a full Draft Amended Report will be presented at an upcoming meeting.

Re-Review – Phytantriol - History and New Data

(Regina Tucker – December 2022 meeting)

Ingredient (1)	Citation	Conclusion	Use - New Data	Use -Historical Data	Notes
Phytantriol	IJT 26 (suppl. 1): 107-114, 2007	Safe as a cosmetic ingredient in the practices of use and concentration	Phytantriol frequency of use (2022): 82 uses conc of use (2022): .001-0.54%	Phytantriol frequency of use (2002): 94 uses conc of use (2003): 0.0001-0.5%; ≤3.0%* *3% was based on expected use in products under development	Frequency of use has decreased. Concentration of use has also decreased.

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Brasch, J., Lipowsky, F., and Kreiselmaier, I. (2008), Allergic contact dermatitis to phytantriol. Contact Dermatitis, 59: 251-252.	Case study	A 44-yr-old woman with no past medical history and no exposure to known irritants presented with acute eczematous skin reactions on the face after utilizing a face cream with Phytantriol. Patch testing revealed Phytantriol as the source of the contact allergy at concentrations 0.02-0.5%.	Yes. No case studies included in original report.

Search (from 2000 on)

PubMed

((("phytantriol") OR (74563-64-7[EC/RN Number])) AND (("2000"[Date - Publication]: "3000"[Date – Publication]))) – 184 hits; 1 useful hit

Current and historical frequency and concentration of use according to duration and exposure for Phytantriol

	# of Uses		*Max Conc of Use (%)*	
	2022[1]	**2002[2]**	**2022[3]**	**2003[2]**
Totals*	**82**	**94**	**0.001-0.54**	**0.0001-0.5; ≤3.0[d]**
Duration of Use				
Leave-On	*46*	*49*	*0.00001 – 0.0054*	*0.0001 - 0.5; ≤ 3.0[d]*
Rinse-Off	*36*	*52*	*0.0001 – 0.005*	*0.002 – 0.1; ≤ 3.0[d]*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR; ≤ 3.0[d]*
Eye Area	10	NR	NR	NR
Incidental Ingestion	1	6	0.0025	NR
Incidental Inhalation-Spray	17;2[a];2[c]	26;1[a];1[c]	0.018 – 0.0054; 0.002[b]	0.0001 – 0.1; 0.1 – 0.2[c]; ≤ 3.0[d]
Incidental Inhalation-Powder	2[c]	1[c]	NR	0.1 – 0.2[c]; ≤ 3.0[d]
Dermal Contact	13	3	0.0001 – 0.002	0.05 – 0.5; ≤ 3.0[d]
Deodorant (underarm)	NR	NR	NR	0.5
Hair - Non-Coloring	58	80	0.0001 – 0.0054	0.0001 – 0.1; ≤ 3.0[d]
Hair-Coloring	NR	NR	NR	NR
Nail	1	5	0.0001 – 0.0025	1.0; ≤ 3.0[d]
Mucous Membrane	2	6	0.0025	0.05; ≤ 3.0[d]
Baby Products	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[d] Presented as anticipated use concentration; the conclusion that was reached considered use as up to 3%.

NR – no reported use

REFERENCES

1. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). 2020. Voluntary Cosmetic Registration Program - Frequency of use of Cosmetic Ingredients. College Park, MD. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2022; received January 11, 2022

2. Andersen FA. Final amended report on the safety assessment of Octyldodecyl Stearoyl Stearate. *Int J Toxicol.* 2005;24 Suppl 3:65-74.

3. Personal Care Products Council Concentration of use by FDA Product Category: 2020 Octyldodecyl Stearoyl Stearate. Unpublished data submitted by the Personal Care Products Council on October 13, 2020

International Journal of Toxicology, 26(Suppl. 1):107–114, 2007

ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810601163947

Final Report on the Safety Assessment of Phytantriol[1]

Phytantriol is an alcohol used in around 100 cosmetic products at concentrations ranging from 0.0002% to 1.0%, although uses at concentrations up to 3% are under development. Phytanriol is supplied at 95.2% and 96.0% purity. Impurities include water, sulphated ash, heavy metals, and a diastereomer of Phytantriol, 3,7,11,15-tetramethyl-1,2,3,4-tetrahydroxyhexadecane. Dermal penetration is low; skin permeability was calculated as log $K_p = -1.734$. Oral LD_{50} values in mice and rats were reported to be >5000 mg/kg. Ocular application of 100% Phytantriol did cause severe corneal damage in some animals, at 23% in diethyl phthalate only slight corneal opacity was seen, and at 10% transient opacity was seen, which resolved by 48 h. Phytantriol at 100% was a severe skin irritant in animal tests. Phytantriol at 3% and 10% in diethyl phthalate produced only slight erythema, which cleared by 48 h. Phytantriol, in the Longhorn egg chorioallantoic membrane assay, was found to have almost no irritation potential when tested at 3% concentration in corn oil. Phytantriol at 25% did produce sensitization in a maximization test, but concentrations of 1% and lower did not cause a sensitization response. Phytantriol is neither phototoxic nor photoallergenic. Phytantriol did not induce aberrations in cultured human lymphocytes, when tested within cytotoxicity limits, nor was it mutagenic in Ames tests, with or without metabolic activation. None of 101 human volunteers reacted initially or to challenge patches of 3% Phytantriol in corn oil. In another investigation of 227 volunteers induced and challenged with 3% Phytantriol in 70:30 ethyl alcohol/water, one person had a mild reaction to the first induction patch; this was the only positive reaction during the induction and challenge phases for all of the volunteers. Phytantriol had no adverse effects in any of 206 volunteer subjects in a repeat insult patch test at 5%. Although data were not available with which to assess reproductive and developmental toxicity and carcinogenic potential, there were no structural alerts suggesting that these end points should be of concern. Dermal penetration is low, and Phytantriol is not genotoxic. Although products containing this ingredient may be aerosolized, typical particle sizes for cosmetic aerosol products are larger than are respirable. Although this ingredient can be irritating and produce sensitization reactions at high concentrations, such effects are absent at lower concentrations. The Panel concluded that cosmetic products could be formulated at concentrations as high as 3% without significant irritation or sensitization.

Received 28 July 2006; accepted 27 November 2006.
[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Address correspondence to Valerie C. McLain, Scientific Analyst and Writer, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

INTRODUCTION

Phytantriol is a cosmetic ingredient used, most often, in hair care preparations and, less often, in skin and nail preparations. This report presents the available data relevant to the assessment of the safety of the use of Phytantriol in cosmetics.

CHEMISTRY

Definition and Structure

As described in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Phytantriol (CAS no. 74563-64-7) is an aliphatic alcohol that conforms to the empirical formula: $C_{20}H_{42}O_3$ and the structural formula shown in Figure 1.

Trade names of Phytantriol include: curasan, haircare complex CLR, AEC phytantriol, PTL, C20-triole, panteen, and PTR (Roche 1999; Gottschalck and McEwen 2004).

Technical names are 3,7,11,15-tetramethyl-1,2,3,-hexadecanetriol and tetramethyl trihydroxyhexadecane (Gottschalck and McEwen 2004) and 3,7,11,15,-tetramethyl-1,2,3,-trihydroxyhexadecane (DSM Nutritional Products 2004a).

Table 1 presents the physical and chemical properties of Phytantriol.

Method of Manufacture

Phytantriol is made from isophytol by oxidation in formic acid, hydrolysis with an inorganic base, such as sodium hydroxide, and isolation from the reaction mixture (Roche 2001).

Impurities

A certificate of analysis included in the studies on the ability of Phytantriol to induce chromosome aberrations carried out by Kumaravel et al. (2004) stated that the Phytantriol used was 95.2% pure; the sample also contained 0.10% water, 0.09% sulphated ash, and ≤20 ppm heavy metals. A similar certificate of analysis included in repeated patch testing with Phytantriol (Consumer Product Testing Co. 2004) lists the sample as 96.0% pure, with 0.09% water, 0.07% sulphated ash, and ≤20 ppm heavy metals.

According to DSM Nutritional Products (2004a), gas chromatography analysis of Phytantriol identified two peaks for 3,7,11,15-tetramethyl-1,2,3-trihydroxyhexadecane representing different diastereomers (DSM Nutritional Products 2004a). 3,7,11,15-tetramethyl-1,2,3,4-tetrahydroxyhexadecane

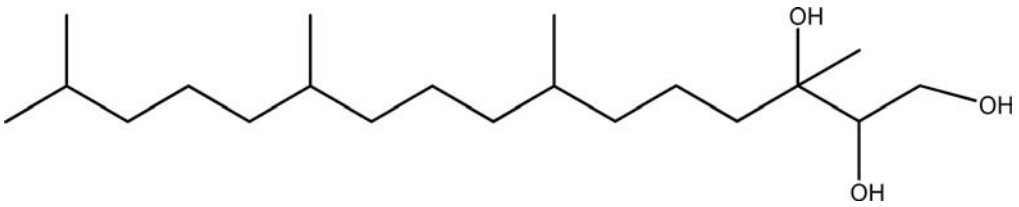

FIGURE 1
Structural formula for Phytantriol (Gottschalck and McEwen 2004).

was also found. This compound differs from Phytantriol in that it has a hydroxy group in position 4, resulting in five chirale C-atoms, as opposed to 4 chirale C-atoms in Phytantriol.

A Derek data base report for 3,7,11,15-tetramethyl-1,2,3,4-tetrahydroxyhexadecane tested all alerts in humans with endpoints of thyroid toxicity, miscellaneous end points, carcinogenicity, irritation, mutagenicity, respiratory sensitization, and skin sensitization. No alerts were found (DSM Nutritional Products 2004b).

USE

Cosmetic

In the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), the functions of Phytantriol in cosmetics include anticaking agent, hair-conditioning agent, and skin-conditioning agent—miscellaneous.

According to Roche (2000b), Phytantriol is used as an ingredient in shampoos, conditioners, setting lotions, hairsprays, hair tonics, gels, and creams. These cosmetic uses are consistent with uses reported to FDA (2002) industry-wide.

Roche (2002a) reported that Phytantriol is used in day and night creams, hand creams, face tonics, body lotions, lipsticks, sun protection products, after-sun products, nail care creams, and nail varnishes. No uses of Phytantriol in suntan products, however, were reported to FDA (2002).

Table 2 gives the uses of Phytantriol reported by industry to FDA (2002) and current concentrations of use provided by CTFA (2003). For example, Phytantriol reportedly is used in 30 of 651 hair conditioners in the concentration range from 0.002% to 0.1%. In some cases, current information on concentration of use is not available, as is the case for nail polishes and enamels. In the case of rouges, a current concentration of use was reported, but no uses were reported to FDA. It is assumed that Phytantriol is used in at least one rouge.

In addition to the reported uses of Phytantriol in cosmetic products, other cosmetics uses under development are given in Table 2 (Davidovich 2004). Ruess (2004) has indicated that at use concentrations up to 3%, Phytantriol may be used in the following leave-on and rinse-off product categories: bath preparations; eye makeup; fragrances; noncoloring hair preparations; hair-coloring preparations; makeup; nail care products; personal hygiene products; shaving preparations; skin care creams, lotions, and powders; and suntan preparations.

The European Union On-line (2000) lists Phytantriol as a cosmetic ingredient; it is classified as a humectant with no restrictions. Phytantriol (EINECS no. 277 923 2) is recognized by the European Inventory of Existing Commercial Chemical Substances and there are no restrictions or safety information provided.

TABLE 1
Physical and chemical properties of Phytantriol (Roche 1999, unless otherwise specified)

Molecular mass	330.55 g/mole
Characterization	Long-chain 1,2,3-trialcohol
Description	Pale yellow or clear liquid, viscous
Odor	sweetish
Density	0.905 g/cm^3
Solubility	Soluble in water, ethanol, and propylene glycol
Refractive index At 589 nm (20°C)	1.470 (Kumaravel et al. 2004)
Melting point	5–10°C
Boiling point	145°C (1.45×10^{-5} psi) $>$ 300°C (14.69 psi)
Skin permeability	log $Kp = -1.734$
Partition coefficient	log $P = 4.228$ (DSM Nutritional Products 2004b)

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Csato (1997b) determined the penetration of Phytantriol in three different formulations using domestic pig skin. Ethanol, polyethylene glycol (PEG 400), and paraffin oil containing 0.5% Phytantriol were used. Phytantriol was labeled with ^{3}H so that the specific radioactivity was 20 μCi/g in each of the final formulations. With a spatula, each formulation was applied at a

TABLE 2
Frequency of use and use concentrations of Phytantriol in cosmetics as a function of product categories

Product category (total number of formulations) (FDA 2002)	Number of products with ingredient (FDA 2002)	Concentration of use (%) (CTFA 2003)
Bath preparations		
Other bath preparations	—	0.05, ≤3.0[a]
Noncoloring hair preparations (196)		
Hair conditioners (651)	30	0.002–0.1, ≤3.0[a]
Hair sprays (aerosol fixatives) (275)	4	0.0001–0.1
Shampoos (884)	22	0.002–0.1, ≤3.0[a]
Hair tonics, dressings, etc. (598)	15	0.0001, ≤3.0[a]
Other noncoloring hair preparations (277)	9	—
Makeup		
Lipstick (962)	6	0.1
Rouges (28)	—	0.1
Other makeup preparations (201)	1	—
Nail care products		
Base coats and undercoats (44)	2	≤3.0[a]
Polishes and enamels (123)	2	≤3.0[a]
Other nail care preparations (55)	1	1.0, ≤3.0[a]
Personal hygiene products		
Underarm deodorants (247)	—	0.5
Other personal cleanliness products	—	0.05
Shaving preparations		
Aftershave lotions (231)	—	0.05, ≤3.0[a]
Skin care preparations		
Face and neck skin care preparations (310)	1	0.1–0.2, ≤3.0[a]
Moisturizers (905)	1	≤3.0[a]
Total uses/ranges for Phytantriol	94	0.0001–3.0

[a]Davidovich 2004.

dose of 6 mg/cm^2 to a 5-cm^2 area on a flap of viable pig skin. Skin samples were clamped into penetration chambers, with the lower part of the skin in constant contact with the receptor phase (physiological salt solution or other medium—not specified). The penetration of each formulation into the skin was evaluated at 1, 6, and 18 h.

All formulations penetrated into the horny and living layers of the skin. The highest penetration was observed with Phytantriol dissolved in ethanol. At 18 h, penetration values in the stratum corneum and in the living skin tissue for the ethanol formulation were 10.0 μg/cm^2 and 1.6 μg/cm^2, respectively. The percent of the applied dose from the ethanol mixture found in the horny layer and living tissue at 1, 6, and 18 h was 20.8%, 19.5%, and 33.5% and 3.6%, 3.3%, and 5.4%, respectively. There was 54.9%, 59.0%, and 43.7% of the applied dose remaining on the surface of the skin at 1, 6, and 18 h, respectively.

The PEG formulation resulted in 94.2%, 76.9%, and 77.4% of the applied dose remaining on the skin at 1, 6, and 18 h. Minimal amounts of 4.8%, 12.3%, and 14.3% and 0.5%, 2.0%, and 2.3% were found in the horny layer and living tissue at 1, 6, and 18 h, respectively. The paraffin oil formulation remained on the skin at 1,6, and 18 h as 83.5%, 80.9%, and 59.4% of the applied dose. Penetration into the horny layer and living skin tissue was 7.4%, 8.9%, and 8.1% and 1.5%, 1.1%, and 1.0% at 1, 6, and 18 h, respectively. Almost no penetration into the chamber fluid was seen for any of the formulations (Csato 1997b).

DSM Nutritional Products (2004b) gave the Phytantriol skin permeability, as calculated by the Potts and Guy equation, as $\log K_p = -1.734$. The partition coefficient, calculated by the Moriguchi estimation, was $\log P = 4.228$.

Penetration Enhancement

Roche (2000b) demonstrated increased penetration of ^{14}C-labeled Panthenol into the hair shaft with the addition of 0.1% Phytantriol. In normal and permanently waved hair, 116 μg/g and 653 μg/g more Panthenol was deposited in the hair due to the Phytantriol-treated shampoo. An increased deposition of 0.5% ^{14}C-labeled keratin amino acids was also illustrated. With an addition of 0.1% Phytantriol, 185 μg/g more amino acids were deposited.

ANIMAL TOXICOLOGY

Roche (1999) reported oral LD_{50} values for Phytantriol of >5000 mg/kg in the mouse and rat, but no experimental details were provided.

A Derek data base analysis of Phytantriol tested for all alerts in humans with super end points of thyroid toxicity, miscellaneous end points, carcinogenicity, irritation, mutagenicity, respiratory sensitization, and skin sensitization based on structure (DSM Nutrional Products 2004b). No alerts were found.

Ocular Irritation

Klecak (1991c) used New Zealand Albino rabbits to test the eye irritation potential of Phytantriol. Only animals with no sign of ocular injury or irritation were used in the testing; three male and three female rabbits were tested. A single dose of 100% Phytantriol was instilled into the left eye of all male rabbits and 23% Phytantriol in diethyl phthalate into the right. The 10% and 3% Phytantriol in diethyl phthalate solutions were instilled into the left and right eyes of the females, respectively. The dose volume was 0.1 ml for each concentration. The lids were held together for about 1 s after application. The eyes of all rabbits were examined at 1, 24, 48, and 72 h, as well as at 7 and 14 days.

Administration of 100% Phytantriol caused slight to severe corneal opacity between 1 and 72 h of observation; this concentration was considered moderately irritating. The 23% concentration caused slight corneal opacity at 1 h, but it returned to generally slight diffuse corneal opacity between 24 and 72 h after test article application; this concentration was slightly irritating. The 10% and 3% concentrations generally caused only slight erythema, which cleared by 48 h; these doses were considered nonirritating. No staining of the cornea and sclera was seen in any of the treated eyes of the test animals throughout the study (Klecak 1991c).

Shapiro (1995) investigated the irritant potential of Phytantriol using white Leghorn eggs. The eggs were incubated for 10 days, and then their shells were removed down to the shell-membrane junction. The inner egg membrane was hydrated with warm saline solution, and then removed after 2 to 5 min. The inner egg membrane was removed to expose the chorioallantoic membrane (CAM). A 0.3-ml aliquot of Phytantriol (3% w/w in corn oil), or one of two controls (Aussie Mega shampoo with papaya or Johnson's baby shampoo) was added to each of four CAMs. The CAMs were rinsed 20 s later with 5 ml of saline. CAMs were observed prior to administration as well as 30 s, and 2 and 5 min after exposure. Reactions of the CAM, blood vessels, and albumin were examined.

Phytantriol had lower irritation scores than both control shampoos. The average irritation score for Phytantriol was 1.75, signifying practically no irritation potential (Shapiro 1995).

Dermal Irritation and Sensitization

Csato and Chubb (1996) used New Zealand albino rabbits to test the dermal irritation of neat Phytantriol. In a preliminary test, one rabbit was clipped free of hair on the dorsal surfaces of the trunk. The following day, a 0.5-ml aliquot of undiluted Phytantriol was placed on a square patch of surgical lint, which was then applied to the clipped flank. The patch was removed 4 h later and the site was rinsed with water. The test site was evaluated 1, 24, 48, and 72 h as well as 7 and 14 days after dosing.

After 1 h, there was evidence of moderate to severe erythema, which persisted through the 72-h examination. Seven days after dosing, the erythema was still present with no reduction in intensity. At this time, slight eschar formation had occurred and the edema raised the skin by about 2 mm. At the final examination, 14 days after dosing, the erythema was barely perceptible, the edema had subsided, and the eschar had healed. The primary irritation index calculated from this one animal was 5.5, which is classified as a severe irritant.

Due to the severity of the reaction to Phytantriol in this one animal, no further animal testing was carried out. The authors concluded that Phytantriol is a severe irritant when applied to the skin of the albino rabbit as in these testing conditions (Csato and Chubb 1996).

Csato and Karanuaratne (1996) conducted a study in which 30 young, female, 464- to 556-g, Dunkin-Hartley guinea pigs (20 test and 10 control) were clipped of hair on the dorsal region between the shoulders. Each animal received three pairs of intradermal injections of 0.1 ml. The test group received (1) 50% v/v Freund's complete adjuvant (FCA) emulsified in water; (2) 5% v/v test article in light liquid paraffin; and (3) 5% v/v concentration of the test article in 1:1 emulsion of FCA and water. The control group received (1) 50% v/v FCA emulsified in water; (2) light liquid paraffin; and (3) 50% concentration of light liquid paraffin in a 1:1 emulsion of FCA and water. Twenty-four hours after these injections, animals were examined.

Test animals had moderate irritation at the injection sites while control animals had minimal to moderate skin irritation at the sites at 24 h.

Six days after the intradermal injection, the control group was treated with 0.5 ml of 10% sodium lauryl sulfate in light liquid paraffin in order to mimic the irritant response expected in the test group. Twenty-four hours later, patches of filter paper were saturated with a 50% v/v concentration of Phytantriol in ethanol and placed over the injection sites of the test animals. The patches were left in place for 48 h and 24 h after removal, the animals were examined for irritation.

Animals in both the control and test groups had minimal to moderate skin irritation at the test site. Fourteen days later, the hair was clipped again and patches with 25% v/v Phytantriol (the maximum nonirritant concentration, as determined during a preliminary ranging study) were placed on the left flank of all animals. The right flank was treated with ethanol. Patches were removed after 24 h and the site was examined at 24 and 48 h after removal.

The challenge application caused a positive response to 25% v/v Phytantriol in 8 (40%) of the 20 test guinea pigs at the

24- and/or 48-h periods. None of the control animals reacted to the 25% v/v Phytantriol challenge. The authors considered Phytantriol a moderate sensitizer in the guinea pig (Csato and Karanuaratne 1996).

Csato (1997a) used the open epicutaneous test (OET) on GOHI (SPF) strain albino guinea pigs, weighing 330 to 470 g, to test the skin sensitization potential of Phytantriol. The induction phase involved applying ethanol or 3%, 10%, 30%, or 50% Phytantriol in ethanol epicutaneously to the right flank of each of six animals 5 days a week for 4 weeks. Sites were left open between applications. The first challenge was carried out 4 weeks after the induction period began. Phytantriol, at concentrations of 0%, 1%, 3%, 5%, and 10% in ethanol, was applied to the shaved left flank. Two weeks later, a second challenge of 0.1%, 0.3%, 1%, 3%, and 5% Phytantriol in ethanol was carried out. Observations were made daily during the induction period as well as 24 and 48 h after challenges were applied.

Phytantriol produced dose-dependent, slight to strong irritant skin reactions during the induction period. Sensitization occurred during both sensitization periods and was generally seen with challenge concentrations of 3% Phytantriol or higher. In sensitized animals, concentrations of 1% and lower did not create an elicitation response.

The author concluded that Phytantriol has skin irritation potential and can cause sensitization in guinea pigs at challenge concentrations of $\geq$3%. The investigator concluded that since concentrations of $\leq$1% did not cause reactions in sensitized guinea pigs, it is unlikely that Phytantriol will produce sensitization in humans at this concentration (Csato 1997a).

Phototoxicity and Photoallergenicity

Phototoxicity testing of Phytantriol was carried out using 15 female SPF-quality guinea pigs, weighing 366 to 447 g; 5 served as a control group (Klecak 1991a). All animals were fasted for 24 h prior to application. Animals were shaved of hair on both flanks, then sedated with 0.2 ml/kg of combelen and narcotized with 0.2 ml/kg of vetanarcol. Four test sites were marked on each flank with a circular stamp. Pretreatment with 2% dimethyl sulphoxide (DMSO) in ethanol (0.025 ml/2 cm^2) took place at 55 and 30 min prior to testing. Then, 0.025 ml of Phytantriol at concentrations of 3%, 10%, 30%, and 100% in ethanol was applied to the left flank. Ten minutes later, the left flank was exposed to nonerythematogenic ultraviolet A (UVA) irradiation at 20 J/cm^2. The right flank was identically treated with Phytantriol but was not exposed to irradiation and was not pre-treated. The control group was treated with ethanol alone. The test sites were examined 24, 48, and 72 h after application of the test substance.

Phytantriol did not cause erythema at doses of 3% and 10%. At 30%, erythema was seen on 2 sites out of 10 on the left and 2 out of 10 on the right flank. The 100% dosage caused erythema in 20 out of 30 sites on the left flank and 20 out of 30 on the right. Phytantriol caused the same amount of irritation in the UV-irradiated and nonirradiated test sites and is not considered phototoxic (Klecak 1991a).

Klecak (1991b) reported a study in which 30 female (10 control) SPF-quality guinea pigs, weighing 263 to 427g, were shaved in the nuchal skin area in preparation for testing the photoallergenicity of Phytantriol. Each animal received four 0.1 ml intradermal injections of Freund's complete adjuvant and saline (1:1) at the four corners of a 6- to 8-cm^2 area of skin. Then, 0.1 ml of 10% Phytantriol in ethanol was applied epicutaneously to the entire area of the test animals; the control animals were left untreated. Test animal sites were exposed to 0.8 J/cm^2 UVB and 10 J/cm^2 UVA irradiation. Topical application followed by irradiation was repeated on days 3, 7, 9, and 11 of the test period.

Three weeks after induction began, all guinea pigs were fasted for 24 h and shaved on both flanks. The animals were then sedated with 0.2 ml/kg combelen and narcotized with 0.2 ml/kg vetanarcol and the test site was marked with a 2-cm^2 stamp. Phytantriol at challenge concentrations of 10%, 30%, and 100% in ethanol was applied to the left flank at a dose of 0.025 ml/2 cm^2 to test and control animals. The flank was then exposed to 10 J/cm^2 UVA irradiation. The right flank was also challenged with Phytantriol, as the left flank was, but was not exposed to irradiation. The test sites were evaluated 24, 48, and 72 h after exposure.

The initial intradermal application areas of the control and test groups had erythema and edema from days 2 to 6, necrosis from days 7 to 14, dessication from days 15 to 21, and exfoliation from day 22 through the end of the test period. The control group also had staining of the area treated with Phytantriol. The test group had staining from days 7 to 13 and 22 to 29. The highest nonirritating concentration found for the challenge application was 10% Phytantriol. No differences were seen between the irradiated and nonirradiated sites, supporting the author's conclusion that Phytantriol is not photoallergenic (Klecak 1991b).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No published studies on the reproductive and developmental toxicity of Phytantriol were available.

GENOTOXICITY

Gocke (2003) tested the genotoxicity of Phytantriol in *Salmonella typhimurium* strains TA1535, TA97, TA98, TA100, and TA102 with and without S9 metabolic activation. Phytantriol was dissolved in DMSO for all testing. The preincubation assay tested Phytantriol at concentrations of 0, 15.8, 50, 158, 500, and 1580 μg/plate and the standard plate incorporation assay tested concentrations of 0, 50, 158, 500, 1580, and 5000 μg/plate. During dose selection, toxic effects were not apparent for concentrations from 0 to 5000 μg/plate; however, precipitation was visible at $\geq$500 μg/plate. No increase in the number of revertant colonies was observed; Phytantriol was not mutagenic in any of the strains with or without metabolic activation.

Kumaravel et al. (2004) tested the effects of Phytantriol (95.2% pure) dissolved in anhydrous DMSO on chromosome aberrations using duplicate human lymphocyte cultures prepared from the pooled blood of three female donors in two experiments. The in vitro cytogenetics assay tested a range of concentrations of Phytantriol from 4.5 to 600 μg/ml in the presence and absence of activation by rat liver postmitochondrial fraction (S9) from Aroclor 1254 induced animals. DMSO was used as a negative control, whereas 4-nitroquinoline 1-oxide (NQO) and cyclophosphamide (CPA) were used as positive controls with and without S9 activation, respectively.

In the first experiment, cultures were treated with 4.5 to 600 μg/ml Phytantriol with and without S9 activation for 3 h, followed by a 17-h recovery period before harvest. Concentrations of 33.79, 45.05, and 60.07 μg/ml without activation and 60.07, 80.09, and 106.80 μg/ml with activation were chosen for analysis to determine concentrations inducing 50% inhibition.

Treatment in the absence of activation caused a steep toxicity profile in which concentrations of 60.07 and 80.09 μg/ml caused 47% and 78% mitotic inhibition, respectively. With activation, Phytantriol (106.8 μg/ml) induced approximately 67% mitotic inhibition.

In the second experiment, treatment without S9 was continuous for 20 h and the concentrations tested were from 30.88 to 150.0 μg/ml with activation. Testing was carried out for 3 h followed by a 17-h recovery and test concentrations ranged from 18.24 to 109.4 μg/ml. Chromosome aberrations were considered cells with structural aberrations and polyploid, endoreduplicated, or hyperdiploid cells. The number of aberrations was determined at concentrations of 47.07, 52.30, and 58.11 μg/ml as well as 95.0, 100.0, and 105.0 μg/ml without and with activation, respectively.

Without activation, 58.11 μg/ml Phytantriol induced approximately 57% mitotic inhibition. A concentration of 105.0 μg/ml caused about 52% inhibition. In the presence and absence of S9 activation, treatment with Phytantriol generally resulted in frequencies of cells with numerical aberrations that were comparable to those within the historical negative-control range. Also, Phytantriol treatment resulted in frequencies of cells with structural aberrations similar to those in concurrent negative controls. The number of aberrant cells (excluding gaps) in treated cultures were within historical negative control ranges. The authors concluded that Phytantriol did not induce chromosome aberrations in cultured human lymphocytes when tested to its limit of cytotoxicity (Kumaravel et al. 2004).

CARCINOGENICITY

No published studies on the carcinogenicity of Phytantriol were available.

CLINICAL ASSESSMENT OF SAFETY

Bull (1995) tested 11 female volunteers, between the ages of 32 and 48, to determine the phototoxicity of Phytantriol. Three test sites were outlined on the lower back with a skin marker; two were marked for the test product while the other remained untreated. About 0.2 ml of 3.3% w/w Phytantriol in corn oil was applied to a patch, which was then adhered to the appropriate test site. Patches were removed after 24 h and one of the treated as well as the untreated site were exposed to timed UVA exposures to achieve a minimal erythemal response (exposure time was based on a preliminary study). All sites were examined 15 minutes as well as 24 and 48 h after irradiation. There were no significant differences between the treated, irradiated sites and the nontreated irradiated sites. The author concluded that Phytantriol was not considered phototoxic.

Roche (1999) reported that no toxic effects have been found in workers handling Phytantriol.

Dermal Irritation and Sensitization

A group of 101 volunteers, aged 17 to 71 years, were patch tested to determine the sensitization potential of Phytantriol (Eisenberg 1995). About 0.2 ml of a solution of 3% w/w Phytantriol in corn oil was applied to a 0.75-square-inch piece of gauze, which was then applied to the upper back as an occluded patch. On Mondays, Wednesdays, and Fridays, this procedure was repeated for a total of 10 applications. Rest periods were 24 h after Tuesday and Thursday removal and 48 h after Saturday removal. A period of 14 days followed the last application, at which time a challenge patch (3% Phytantriol in corn oil) was applied to the original site as well as to a new site on the forearm. These sites were examined 24 and 48 h later. Rechallenge patch testing was carried out on anyone exhibiting a response during the challenge period to confirm the prior results.

There were no positive reactions for any of the volunteers throughout the study. The author concluded that Phytantriol at a 3% concentration in corn oil was neither a dermal irritant nor sensitizer (Eisenberg 1995).

The Consumer Product Testing Co. (2004a) selected 227 male and female subjects (age 16 to 79 years) for repeated-insult patch testing. None of the volunteers had any visible skin diseases or history of adverse reactions to cosmetics and other personal care products. Phytantriol (96.0% pure) was tested at 3% in a 70:30 ethyl alcohol/deionized water solution. Application involved allowing about 0.2 ml of test material to dry for 30 min onto a 3/4 $\times$ 3/4-inch absorbent pad portion of an adhesive dressing. The occluded patch was then applied to the upper back between the scapulae.

During the 3-week induction phase, patches were applied on Mondays, Wednesdays, and Fridays for a total of 9 applications. Rest periods were 24 h long following each Tuesday and Thursday removal and 48 h after each Saturday removal. Induction patches were applied for 24 h and the site was scored after each removal.

The challenge phase took place approximately 2 weeks after the final induction patch application; a challenge patch was applied to a new test site adjacent to the original induction patch

site and the same procedure was used. The patch was removed and the site scored 24 and 72 h after application. Test sites were scored on a scale from 0 to 4.

Only one person had a positive (score = 1) reaction after the first induction patch was removed. A score of 1 was described as mild erythema covering most of the test site. This was the only positive score for this person and was the only positive score for both the induction and challenge phases for all volunteers. The authors stated that Phytantriol did not indicate a potential for dermal irritation or allergic contact sensitization (Consumer Product Testing Co. 2004a).

The Consumer Product Testing Co. (2004b) conducted a repeated-insult patch test (RIPT) in 226 eligible volunteers, both male and female, ranging from 16 to 79 years of age. Although there were 226 qualified subjects, only 206 volunteers completed the study. The remaining subjects discontinued the study for various reasons, none of which are related to the application of the test material.

A concentration of 5% Phytantriol (diluted in 70% alcohol) was used. The patch was applied to the skin site three times per week for a total of nine applications. There were no visible skin reactions found in any of the subjects at this particular concentration. About 2 weeks following the final induction patch application, a challenge patch was applied to a virgin test site next to the original induction patch site, using the same guidelines described for induction. Twenty-four and 72 h post application, the patch was removed and the site was scored.

The authors stated that 5% Phytantriol in a 70:30 ethanol/deionized water solution did not have a potential for dermal irritation or allergic contact sensitization (Consumer Product Testing Co. 2004b).

SUMMARY

Phytantriol is an alcohol used, most often, in hair care preparations and, less often, in skin and nail preparations. Phytantriol is reportedly used in 94 cosmetic products at concentrations ranging from 0.0002% to 1.0%, although uses at concentrations up to 3% are under development. Phytanriol is supplied at 95.2% and 96.0% purity. Impurities include water, sulphated ash, heavy metals, and a diastereomer of Phytantriol, 3,7,11,15-tetramethyl-1,2,3,4-tetrahydroxyhexadecane.

Dermal penetration was low in an in vitro study of Phytantriol using pig skin. Skin permeability was calculated as log $K_p = -1.734$ and the partition coefficient as log $P = 4.228$.

Oral LD_{50} values in mice and rats were reported to be >5000 mg/kg.

Ocular application of 100% Phytantriol caused severe to slight corneal opacity in albino rabbits. Phytantriol at 23% in diethyl phthalate produced slight corneal opacity, which reduced over time, and was considered slightly irritating. Phytantriol at 3% and 10% in diethyl phthalate produced only slight erythema, which cleared by 48h. Phytantriol, in the Longhorn egg chorioallantoic membrane assay, was found to have almost no irritation potential when tested at 3% concentration in corn oil.

Dermal irritation testing of 100% Phytantriol in albino rabbits resulted in a cancellation of the experiment after preliminary testing on one rabbit because of severe erythema and edema; a calculated primary irritation index of 5.5 signified a severe irritant.

Sensitization testing with guinea pigs using a maximization test resulted in a positive reaction in 40% of the animals to 25% Phytantriol in ethanol. Further sensitization testing utilizing the open epicutaneous test on guinea pigs suggested that Phytantriol does have sensitization potential. Concentrations of 1% and lower did not cause a sensitization response, but at concentrations higher than 3%, Phytantriol was predicted to induce cutaneous sensitization.

Phototoxicity and Photoallergenicity testing in guinea pigs and humans showed that Phytantriol is neither phototoxic nor photoallergenic.

Phytantriol did not induce aberrations in cultured human lymphocytes, when tested within cytotoxicity limits, nor was it mutagenic in Ames tests, with or without metabolic activation.

None of 101 human volunteers reacted initially or to challenge patches of 3% Phytantriol in corn oil. In another investigation of 227 volunteers induced and challenged with 3% Phytantriol in 70:30 ethyl alcohol/water, one person had a mild reaction to the first induction patch; this was the only positive reaction during the induction and challenge phases for all of the volunteers. Phytantriol had no adverse effects in any of the 206 volunteer subjects who underwent a repeated-insult patch test at a 5% concentration.

DISCUSSION

Although data were not available with which to assess reproductive and developmental toxicity and carcinogenic potential, the Cosmetic Ingredient Review (CIR) Expert Panel noted that Phytantriol is not toxic in acute oral testing, that there were no structural alerts suggesting that these end points should be of concern, and that the available genotoxicity data demonstrated that Phytantriol was not genotoxic. In addition, dermal penetration of Phytantriol is low, consistent with its chemical structure and molecular weight.

The Panel also considered that Phytantriol is used in products that may be aerosolized. Because current technology used for such cosmetics products produces particles that are not respirable, the absence of inhalation toxicity data was not considered relevant.

The Panel noted that severe dermal irritation is seen with 100% Phytantriol in rabbits; minimal to moderate irritation was seen during the induction phase of a guinea pig maximization study using 25% Phytantriol; and cumulative dermal irritation was seen during the induction phase of an open epicutaneous study of Phytantriol at 10% and 30% in ethanol using guinea pigs, but was minimal at 3%. Whereas the guinea pig dermal sensitization studies suggested that allergic reactions were possible at concentrations ≥3%, clinical testing of 3% Phytantriol

in corn oil and in ethanol/water did not demonstrate irritation during induction, nor was there any sensitization at challenge. Phytantriol had no adverse effects in any of the 206 volunteer subjects who underwent a repeated-insult patch test at a 5% concentration. In addition, the Panel noted that Phytantriol tested in guinea pigs at 3.0%, 10%, 30%, and 100% did not produce any phototoxicity or photoallergenicity reactions. Taken together, the irritation and sensitization data suggested to the Panel that cosmetic products could be formulated at concentrations as high as 3% without significant irritation or sensitization.

CONCLUSION

Phytantriol is safe as a cosmetic ingredient in the practices of use and concentration as described in this safety assessment.

REFERENCES

BASF. 1998. BASF continues to build cosmetic line with three new product introductions. http://www.basf.com/businesses/consumer/cosmeticingredients/html/pr980712.html (accessed February, 2003).

Bull, M. 1995. Phototoxicity. Unpublished data submitted by Roche Vitamins Inc., August 2003.7 pages.[2]

Consumer Product Testing Co. 2004a. Repeated insult patch test with 3% Phytantriol in 70:30 Ethyl Alcohol/Deionized Water Solution. Unpublished data submitted by DSM Nutritional Products, Inc. May 2001. 22 pages.[2]

Consumer Product Testing Co. 2004b. Repeated insult patch test with 5% Phytantriol. Unpublished data submitted by DSM Nutritional Products, Inc. October 11, 2004. 24 pages.[2]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2003. Concentration of use of Phytantriol. Unpublished data submitted by CTFA, July 2003. 1 page.[2]

Csato, M. 1997a. Study of skin sensitization in the Guinea Pig; Open epicutaneous test (Study No. 250D96). Unpublished data submitted by Roche Vitamins Inc, August 2003. 27 pages.[2]

Csato, M. 1997b. Study of penetration in the pig skin in vitro (Study No. 024D97). Unpublished data submitted by Roche Vitamins Inc., August 2003. 22 pages.[2]

Csato, M., and D. R. Chubb. 1996. Acute Dermal Irritation Study with Ro 04-3724/0000 in the Rabbit. Study 936D96. Unpublished data submitted by Roche Vitamins Inc, August 2003. 12 pages.[2]

Csato, M., and S. D. Karunaratne. 1996. Skin sensitization study with Ro 04-3724/000 (Phytantriol) in the Guinea pig. Study 938D96. Unpublished data submitted by Roche Vitamins Inc., August 2003. 17 pages.[2]

Davidovich, A. 2004. Personal communication regarding products in development which may contain up to 3% Phytantriol. 1 page.[2]

DSM Nutritional Products. 2004a. Phytantriol structural analysis. Unpublished data submitted by DSM Nutritional Products, May 2004. 1 page.[2]

DSM Nutritional Products. 2004b. Derek data base report for Phytantriol and 3,7,11,15-tetramethyl-1,2,3,4-tetrahydroxyhexadecane. Unpublished data submitted by DSM Nutritional Products, May 2004. 2 pages.[2]

Eisenberg, R. 1995. Repeated insult patch test. Unpublished data submitted by Roche Vitamins Inc., August 2003. 12 pages.[2]

European Union On-Line. 2000. First update of the inventory of ingredients employed in cosmetic products. http://europa.eu.int/comm/food/fs/sc/sccp/out123cm_en.pdf (accessed March, 2003).

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Gocke, E. 2003. RO0043724-000: Bacterial reverse mutation test (Ames test). Unpublished data submitted by Roche Vitamins Inc., September 2003. 33 pages.[2]

Gottschalck, T. E. and G. N. McEwen, Jr., eds. 2004. *International cosmetic ingredient dictionary and handbook*, 10th ed., Vol. 1–2. Washington, DC: CTFA.

Klecak, G. 1991a. Determination of the photoxicity in albino guinea pigs with Ro 04-3724—Phytantriol L. 804258. Unpublished data submitted by Roche Vitamins Inc., August 2003. 30 pages.[2]

Klecak, G. 1991b. Determination of photallergenicity in albino guinea pigs with Ro 04-3724—Phytantriol L. 804258. Unpublished data submitted by Roche Vitamins Inc., August 2003. 37 pages.[2]

Klecak, G. 1991c. Determination of primary eye irritation in rabbits with Ro 04-3724—Phytantriol L. 804258. Unpublished data submitted by Roche Vitamins Inc., August 2003. 48 pages.[2]

Kumaravel, T. S., A. Chetelat, and E. Wolz. 2004. Phytantriol: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes. Unpublished data submitted by Covance Laboratories. May 2001. 49 pages.[2]

Roche. 1999. Safety Data Sheet for Phytantriol. http://euroweb.roche.com/msds/english/0429082.pdf (accessed February 2003).

Roche. 2000a. Active agents and emulsifiers for beauty care: Borage oil, evening primrose oil, sun filters, emulsifiers, phytantriol. http://www.roche.com/vitamins/pdf/agents.pdf (accessed February 2003).

Roche. 2000b. Phytantriol product brochure. http://www.roche.com/vitamins/pdf/phyt.pdf (accessed February 2003).

Roche Vitamins, Inc. 2001. Information packet on Phytantriol. Unpublished data submitted by Roche. 15 pages.[2]

Ruess, A. J. 2004. Personal communication regarding products in development which may contain up to 3% Phytantriol. 1 page.[2]

Shapiro, O. 1995. The Hen's Egg Test—utilizing the chorioallantoic membrane (HET-CAM). Unpublished data submitted by Roche Vitamins Inc., August 2003. 5 pages.[2]

[2]Available for review from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.