Safety Assessment of Choleth-24 as Used in Cosmetics

Status:	Re-Review for Panel Consideration
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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 safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/ Writer, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Senior Scientific Analyst/Writer, CIR
Date: November 10, 2022
Subject: Re-Review of the Safety Assessment of Choleth-24

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of Choleth-24 in 1982 (identified as *originalreport_Choleth24_122022* in the pdf), with the conclusion that this ingredient is safe for topical applications to humans in the present practices of use and concentration, as stated in that report. The Panel previously considered a re-review of this report and determined to not reopen the assessment, as published; thus, the conclusion published in 2005 was reaffirmed (*rereview2005_Choleth24_122022*).

Because it has been 15 years since the previous re-review was published, in accord with Cosmetic Ingredient Review (CIR) Procedures, the Panel should consider whether the safety assessment of Choleth-24 should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1998 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_Choleth24_122022*).

No new toxicological studies were found in the literature; however, it should be noted that Choleth-24 is an inactive ingredient in two FDA-approved drug formulations. In addition, Choleth-24 is not restricted for use in cosmetics according to the European Union CosIng database.

According to the original (1982) safety assessment, "choleth is the ethoxylated cholesterol fraction of lanolin alcohol. Since lanolin alcohol may contain as much as 38% cholesterol, ethoxylating these alcohols to produce laneths also produces choleths." It should be noted that some sterol-containing PEG ethers (e.g., Laneth-25) contain choleths, and have been reviewed by the Panel. These ethers were last reviewed as part of the safety assessment of alkyl PEG ethers, for which the Panel concluded safe in the present practices of use and concentration as stated in that assessment when formulated to be non-irritating. (Additionally, the 1982 safety assessment of Choleth-24 included data from the 1982 assessment of laneths.)

Also included for your review is a table of current and historical use data (*usetable_Choleth24_122022*). The frequency of use for Choleth-24 has decreased from 191 uses reported in 2002 to 33 uses reported in 2022. In 2002, Choleth-24 was reported to be used at up to 1.3%. No uses were reported for Choleth-24 in a 2022 concentration of use survey performed by Council.

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

Re-Review - Choleth-24 - History and New Data

(Priya Cherian – December 2022 meeting)

Ingredient	Citation	Conclusion	Use - New Data	Results	Use - Existing Data	Results	Notes
Choleth-24	JACT 1(4):119-126, 1982 IJT 24(S1):1-102, 2005	safe as used*not re-opened	frequency of use (2022) conc of use (2022)	33 none reported	frequency of use (2002) conc of use (2002)	191 0.002 – 1.3	frequency of use decreased

*According to the 1982 published report, Choleth-24 was considered safe for **topical application to humans** in the practices of use and concentration as stated in that assessment.

NOTABLE NEW DATA			
Publication	**Data Type**	**Results – Brief Overview**	**Different from Existing Data?**
https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm	ingredients in FDA-approved drugs	Choleth-24 is an inactive ingredient in two FDA-approved pharmaceutical products – a vaginal cream at up to 1% and a topical emulsion at up to 5%	Not included in previous report
https://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.simple	European Union legislation – CosIng	Choleth-24 is not restricted for use in cosmetics according to the EU CosIng database	Not included in previous report

Search (from 1998 on)

PubMed

((("choleth-24") OR (27321-96-6[CAS Number])) AND (("1997"[Date - Publication] : "3000"[Date - Publication])) – 4 hits; none useful

FDA

("choleth-24")

EU COSING

("choleth-24")

Table 1. Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*	
	Choleth-24			
	2022[1]	**2002[2]**	**2022[3]**	**2002[2]**
Totals*	**33**	**191**	**NR**	**0.002 – 1.3**
Duration of Use				
Leave-On	*24*	*140*	*NR*	*0.008 – 1.3*
Rinse-Off	*9*	*49*	*NR*	*0.002 – 1*
Diluted for (Bath) Use	*NR*	*1*	*NR*	*NR*
Exposure Type				
Eye Area	NR	4	NR	0.2 – 0.3
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	12[a]; 7[b]	17; 44[a]; 33[b]	NR	0.3; 0.008 – 1.3[a]; 0.1 – 0.7[b]
Incidental Inhalation-Powder	7[b]	33[b]	NR	0.2; 0.1 – 0.7[b]
Dermal Contact	20	138	NR	0.002 – 1.3
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	5	15	NR	0.2 – 1
Hair-Coloring	7	38	NR	0.5
Nail	1	NR	NR	0.3
Mucous Membrane	NR	2	NR	0.002 – 0.7
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] 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
NR – not reported

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

2. Andersen FA (ed). Annual review of cosmetic ingredient safety assessments - 2002/2003. *IJT.* 2005;24:1-102.

3. Personal Care Products Council. 2022. Concentration of use by FDA product category: Choleth-24. (Unpublished data submitted by Personal Care Products Council on October 24, 2022.)

JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
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Final Report on the Safety Assessment of Choleth-24

Choleth-24 is the polyoxyethylene ether of the cholesterol fraction of lanolins, and is used in cosmetics as a surfactant, dispersant, stabilizer, and emulsifier at concentrations up to 5%. Acute animal studies have shown Choleth-24 to be slightly toxic when ingested, nonirritating to mildly irritating when applied by the Draize method to skin at concentrations of 0.5–100%, and practically nonirritating when instilled in the eyes of rabbits at concentrations up to 100%. Clinical studies have determined Choleth-24 to be only slightly irritating and nonsensitizing when applied to human skin in concentrations up to 50%. Choleth-24 at 0.5% concentration was neither phototoxic nor photoallergenic when tested in 201 subjects. It is concluded that Choleth-24 is safe for topical application to humans in the present practices of use and concentration.

INTRODUCTION

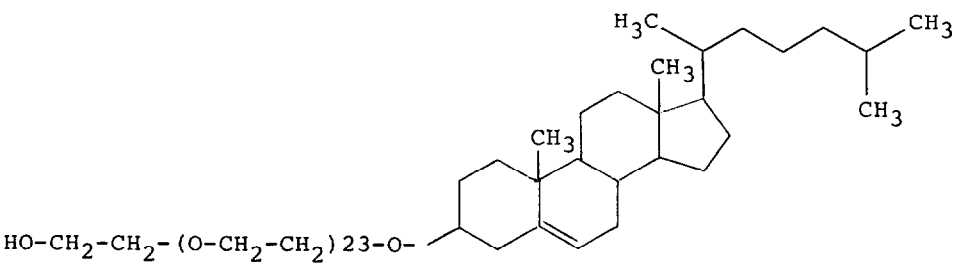
CHOLETH is the ethoxylated cholesterol fraction of lanolin alcohol. Since lanolin alcohol may contain as much as 38% cholesterol, ethoxylating these alcohols to produce Laneths also produces Choleths.[1] For completeness, the safety data on Laneths-5, -16, and -25 have been included in this report.[2]

CHEMISTRY

Structure

Choleth-24 is the polyoxyethylene ether of cholesterol with an average ethoxy chain length of 24. Other names for this ingredient include: PEG-24 Cholesteryl Ether, Polyethylene Glycol (24) Cholesteryl Ether, and Polyoxyethylene (24) Cholesteryl Ether.

Choleth-24 conforms to the following structure:[3,4]



Choleth-24 is prepared by reacting the cholesterol fraction of lanolin alcohol with ethylene oxide in the presence of an alkaline catalyst, until an average of 24 moles of ethylene oxide has been added to each mole of cholesterol. The catalyst is then acid-neutralized and the product vacuum stripped to remove any unreacted ethylene oxide. Choleth-24 is then filtered to remove the insoluble salts that form as a result of catalyst neutralization.[4]

Properties

Choleth-24 is an off-white or pale yellow waxy solid with a faint odor. It is soluble in both water and alcohol and has the properties of a nonionic surfactant (Table 1).[4-7]

Analytical Methods

Spilker and Richey[8] have described a number of analytic techniques useful for the determination of lanolin and lanolin derivatives. These generally involve hydrolysis, fractionation, separation by chromatography, and identification. Infrared spectroscopy (IR) is also used to identify Choleth-24.[9] Scotney and Truter[10] used paper chromatography to determine the components of Choleth-24.

Impurities

Choleth-24 may contain related lanolin alcohols, inorganic salts, and related lanolin sterols such as dihydrocholesterol, 7-keto cholesterol, lanosterol, dihydrolanosterol, and 7-keto lanosterol and possibly ethoxylated forms of these minor lanolin sterols.[1,4] Trace amounts of 1,4-dioxane, a reaction product of the ethoxylation process, may be present, as well as pesticides and trace metals found in crude lanolin.[2]

Additives

The antioxidant/preservative butylated hydroxytoluene (BHT) may be added by the manufacturer to Choleth-24 in concentrations of 0.05%.[4] BHT is a Generally Recognized as Safe (GRAS) ingredient for which regulations have been issued under the Food, Drug and Cosmetic Act (21 CFR 121.101). Its use in food products is limited to 0.02%.

USE IN COSMETICS

Choleth-24 is used in cosmetic products as an emulsifier, stabilizer, dispersant, and nonionic surfactant. The solubility characteristics of cholesterol are changed by ethoxylation. Choleth-24 is used in some oil-in-water lotions to retard the viscosity build-up commonly associated with cholesterol-containing products. The viscosity of anionic lotions can be reduced effectively by the addition of less than 1% Choleth-24.[6,11,12]

TABLE 1. CHEMICAL AND PHYSICAL PROPERTIES OF CHOLETH-24.[a]

Property	*Value*
Hydroxyl value	35–45
Acid value	1.5 (maximum)
Saponification value	3.0 (maximum)
Iodine value	12–19
Moisture	0.5% (maximum)
pH (10% aqueous)	4.5–7.5
Cloud point	88°–95°C
Heavy metals	20 ppm (maximum)
Arsenic	2 ppm (maximum)
Ash	0.25% (maximum)
Hydrophile/Lipophile balance	14

[a]From Refs. 4–7.

Choleth-24 is used in over 130 cosmetic formulations in concentrations up to 5% (Table 2). Products containing Choleth-24 may come in contact with the hair and skin, particularly of the face. These products may be used daily or occasionally and their use may extend over a period of years. Daily contact with Choleth-containing products may last from seconds to all day.[13]

Laneths-5, -16, and -25, which contain Choleths, are used in cosmetics at maximum concentrations of 10%.[2]

BIOLOGICAL PROPERTIES

Animal Toxicology

Acute Oral Toxicity

Five groups of one male and one female albino rat each were administered by gavage a 50% Choleth-24 solution in vegetable oil, in doses of 0.625–10.00 g/kg and observed daily for two weeks. Rats receiving 1.25–10.00 g/kg died within 24 h, whereas all those receiving 0.625 g/kg survived. The approximate acute oral LD50 was determined to be 0.9 g/kg, which corresponds to that of materials classified as slightly toxic.[14,15]

Laneths-5, -16, and -25, which contain Choleths, were administered by gavage to groups of five rats each. Acute oral LD50s for these three ingredients were 25.9–45.0 ml/kg, 9.33–12.2 ml/kg, and >3.0 g/kg, respectively. These resulting LD50s correspond to those of materials classified as practically nontoxic.[2,15]

TABLE 2. FDA PRODUCT FORMULATION DATA FOR CHOLETH-24.[a]

Product type	*Conc. Range (Percent)*	*Number of formulations*
Bubble baths	>1–5	1
Eyeliners	>1–5	14
Eye shadows	>0.1–1	2
Mascaras	>1–5	4
	>0.1–1	2
Other eye makeup preparations	>0.1–1	1
Hair conditioners	>0.1–5	3
	>1–5	3
	>0.1–1	4
Shampoos	>1–5	1
	>0.1–1	2
Tonics and Dressings	>1–5	1
Moisturizers	>0.1–1	2
Night skin preparations	>0.1–1	2
Hair dyes	>0.1–1	71
Blushers	>0.1–1	1
Leg and body paints	>1–5	1
Makeup bases	>0.1–1	1
Other makeup preparations	>1–5	1
Aftershaves	>1–5	1
Skin cleansing preparations	>0.1–1	4
Face, body, and hand preparations	>0.1–1	4
	≤0.1	1
Skin fresheners	>1–5	1
	>0.1–1	1
Other skin care preparations	>0.1–1	8

[a]From Ref. 13.

Primary Skin Irritation

The Draize method was used to test the skin irritancy of undiluted Choleth-24 when applied to the clipped intact and abraded skin of six albino rabbits; irritation was scored at 24 and 72 h. Choleth-24 produced very slight to well-defined erythema in all intact and abraded sites; irritation persisted throughout the 72-hour test period. There was very slight to well-defined edema on all six abraded sites and on four of six intact sites; edema also persisted throughout the test period. The primary irritation index (PII) was 1.29 (maximum score = 8) which indicated mild skin irritation.[16,17]

Motoyoshi et al.[18] compared the skin irritancy of undiluted Choleth-24 in rabbits, guinea pigs, rats, and miniature swine. Choleth-24 was applied to the clipped intact skin of each of six rabbits, rats, and guinea pigs. The test sites were rinsed after 24 h, scored, and the compound reapplied. This procedure was repeated daily for three days. After the final reading, each animal was injected intravenously with 40 mg/kg Evans Blue dye. The animals were sacrificed one hour later and the skin sites excised and scored for erythema, edema, and capillary permeability. In miniature swine, 0.05 g Choleth-24 was applied under an occlusive patch to the shaved intact skin of each of six animals. Patches were removed at 48 h and the skin was evaluated as above. The sum of the averages of the erythema, edema, and capillary permeability scores was referred to as the PII. Choleth-24 was reported to be severely irritating to rabbit skin, moderately irritating to guinea pig and rat skins, and nonirritating to the skin of miniature swine. When these results and those of 19 other cosmetic ingredients were compared to results of human skin patch tests, the authors concluded that in this assay the skin of miniature swine was more reliable than rabbit, rat, or guinea pig skin in screening human skin irritants under their test procedures. The skin irritation test reported by Motoyoshi et al.[18] is not comparable to the Draize test. The former involves a three-day application of the test substance and a scoring system which includes capillary permeability grading; the latter assay contains neither of these procedures. Irritation scores on compounds other than Choleth-24 indicate that values obtained by the methods of Motoyoshi et al. are greater than those obtained under the Draize test.

An eyeliner containing 5% Choleth-24 was tested for skin irritation in three rabbits. Test material was applied daily for four days to the clipped intact and abraded skin of animals. Sites were scored daily for seven days. No skin irritation was observed.[19]

A modified Draize method was used to study the skin irritancy of a nail conditioner containing 0.50% Choleth-24. The product was applied to the clipped intact and abraded skin of six albino rabbits. Skin sites were examined and scored after 24 h and the solution reapplied. This procedure was repeated for three days. There was no reaction in any of the animals.[20]

Undiluted and ten percent Laneths-5, -16, and -25, were tested for primary skin irritation in rabbits. PIIs resulting from application of undiluted materials were: Laneth-5, 0.8 to 1.3; Laneth-16, 1.0 to 2.43; and Laneth-25, 3.83. These values correspond to those of materials classified as slightly to mildly irritating, mildly to moderately irritating, and severely irritating, respectively. The PIIs of 10 percent solutions of these Laneths were 0.04–1.0, or practically nonirritating to mildly irritating to rabbits' skin. Undiluted Laneths-5 and -16 were reported to be nonirritating to rabbits' skin in Department of Transportation tests.[2]

Primary Eye Irritation

The Draize method was used to evaluate the eye irritation of undiluted Choleth-24 on albino rabbits. The test material (0.1 ml) was instilled into the right eye of each of nine animals; the left eye remained untreated. The eyes of three animals were washed with water four seconds after instillation. In the unwashed group, one of six rabbits developed slight conjunctivitis which disappeared by the second day. None of the animals in the washed group developed eye irritation. The average ocular irritation indices (AOIIs) for the washed and unwashed groups were 0.7 and 0, respectively (maximum score = 110).[21]

An eyeliner containing 5 percent Choleth-24 was tested for eye irritation in six rabbits. The test material (0.1 ml) was instilled into each animal's left eye; the right eye served as an untreated control. Eyes were observed daily for one week. Slight conjunctivitis after one hour was observed in some animals but disappeared within 24 to 72 h.[19]

The Federal Hazardous Substance Act (FHSA) method was used to test the eye irritancy of a nail conditioner containing 0.50% Choleth-24. The test material (0.1 ml) was placed in one eye of each of six rabbits; the other eye served as an untreated control. Eyes were examined after 24, 48, and 72 hours; there was no irritation (AOII = 0) and the product was determined to be nonirritating.[20]

Two undiluted and one 10 percent Laneth-5 solutions were tested for primary eye irritation on rabbits. One undiluted and the 10% solutions were nonirritating; in another test, however, undiluted Laneth-5 was minimally irritating.[2]

Undiluted Laneth-16 was instilled into rabbits eyes; some eyes were subsequently washed after instillation. In the washed group, Laneth-16 was nonirritating to minimally irritating. In the unwashed group, Laneth-16 caused minimal irritation; in one study, irritation persisted throughout the seven-day observation period.[2]

Undiluted Laneth-25, instilled into six rabbits' eyes, caused minimal irritation which persisted throughout the seven-day observation period.[2]

Clinical Assessment of Safety

Irritation and Sensitization

A repeated insult patch test was used to study the skin irritation and sensitization of Choleth-24 in 51 human subjects. The subjects were divided into five groups; each group was initially patch-tested with 10%, 20%, 30%, 40%, or 50% Choleth-24 in water. After the fourth application, the concentration was raised to 50% for all subjects. The test material was applied under occlusion for 24 h; the patch was then removed, the site scored, and a fresh patch reapplied. This procedure was repeated four days per week for three weeks for a total of 12 patches. After a rest of 15 days, a 24-hour challenge patch was applied to an untreated site. Sites were scored at 24, 48, and 72 h. There were five reactants (1+ to 2+) to the first four induction patches (10–50% Choleth-24), three of ten subjects at 10%, and two of eleven subjects at 50% Choleth-24. During the next two weeks of induction (all at 50% Choleth-24), eight subjects reacted (1+ to 2+) to one or more patches. No reactions were elicited by challenge patches. It was concluded that 10–50% Choleth-24 is nonirritating to minimally irritating but 50% is capable of being a "fatiguing agent" (a material which elicits a skin response resulting from its cumulative effect on the skin). A concentration of 50% Choleth-24 was nonsensitizing.[22]

Motoyoshi et al.[18] did a comparative study on the irritancy of cosmetic ingredients to the skin of various animals and man. In the human single insult patch tests, undiluted Choleth-24 was applied under occlusion to 50 men for 48 h. Sites were scored 24, 48, and 72 h later. Under an unusual classification scheme, undiluted Choleth-24 was determined to be mildly irritating since it elicited 5 to 20 reactions (including "questionable" responses). The authors concluded that, of the species tested, the irritancy and penetrability of human skin most closely resembles that of miniature swine skin.

A modified Draize-Shelanski-Jordan patch test was used to determine the irritancy and sensitizing potential of a nail conditioner containing 0.50 percent Choleth-24. The test material was applied under occlusion to the upper back of each of 201 subjects. Sites were scored at 48 h and a fresh patch reapplied. This procedure was repeated three days per week for three weeks. Two weeks after the removal of the last induction patch, two consecutive 48-hour challenge patches were applied to a single untested site. Sites were scored at 48 and 96 h. None of the patches, including challenge patches, elicited a reaction. It was concluded that the product was nonirritating and nonsensitizing.[20]

A repeated insult patch test was used to study the irritancy and sensitizing potential of 50 percent aqueous Laneth-5, -16, and -25 solutions. In each study, 50 subjects were divided into five groups of 10 to 12 each. In preliminary studies, each ingredient was tested in concentrations of 10%, 20%, 30%, 40%, and 50%. The test sample was applied four times and the results scored. From these initial studies, one concentration (50%) was selected for the actual test. Test sites were exposed to

sample for four consecutive days, read on the fifth day, and rested the next two days. This protocol was repeated three times and followed by a 15-day rest period. At this time, 24-hour occluded challenge exposures were made at new sites and evaluated for hypersensitivity reactions. Twenty-four, 48, and 72 h later evaluations for delayed hypersensitivity reactions were made at the new sites. It was concluded that 50% Laneth-5, Laneth-16, and Laneth-25 were nonirritating and nonsensitizing, but that Laneth-5 and Laneth-16 were mild "fatiguing" agents.[2]

Photosensitization

A nail conditioner containing 0.5% Choleth-24 was tested for photosensitization in 27 men and women. The test material was applied under an occlusive patch for 24 h; patches were then removed and sites were scored. Skin sites were then irradiated with three minimal erythemal doses of ultraviolet light (200–400 nm) with a xenon arc solar simulator (150 W). Sites were scored 48 h later. The entire procedure was repeated twice weekly for three weeks. Following a 10-day rest period, a challenge patch was applied to a previously untreated site. Sites were scored and irradiated at 24 hours and scored again 15 min and 24, 48, and 72 h post-irradiation. No reactions to any of the patches were observed either before or after irradiation. The investigators concluded that the product containing 0.50% Choleth-24 is nonphototoxic and nonphotoallergenic.[20]

SUMMARY

Choleth-24 is the polyoxyethylene ether of the cholesterol fraction of lanolins with an average of 24 moles ethylene oxide added to each mole of cholesterol. Another related group of cosmetic ingredients, the Laneths, may contain as much as 38 percent Choleth. Choleth-24 is an off-white waxy solid which is soluble in water and alcohol, and acts as nonionic surfactant. Impurities which may be found in Choleth-24 include related lanolin alcohols and sterols, inorganic salts, and 1,4-dioxane. BHT, a GRAS ingredient, may be added by the manufacturer to Choleth-24 at a concentration of 0.05%.

Choleth-24 is used in cosmetics as a surfactant, dispersant, stabilizer, and emulsifier. It is used in concentrations up to 5%. Choleth-containing products may come into contact with most external surfaces of the body and may be applied for a period of years.

Acute animal studies have shown Choleth-24 to be slightly toxic when ingested, nonirritating to mildly irritating when applied by the Draize method to skin at concentrations of 0.5–100%, and practically nonirritating when instilled in the eyes of rabbits at concentrations up to 100%.

Clinical studies have determined Choleth-24 to be nonirritating to mildly irritating and nonsensitizing when applied to human skin in concentrations up to 50%. Choleth-24 (as 0.5% in a nail conditioner) was neither phototoxic nor photoallergenic when tested in 201 subjects.

DISCUSSION

Lanolin alcohol, a saponification product of whole lanolin may contain as much as 38% cholesterol.[1] This cholesterol fraction is ethoxylated to Choleth. When ethoxylated alone, lanolin alcohol produces Laneth, a substance which can contain up to 38% Choleth. This means that data applicable to the safety assessment of the Laneths are also applicable to that of the Choleths. The Expert Panel has already determined the Laneths to be safe at concentrations presently used in cosmetic formulations.[2]

Traces of 1,4-dioxane, a product of the ethoxylation process, may be present as an impurity in Choleth-24. Administration of 1% 1,4-dioxane in drinking water of rats for 13 months induced liver lesions and hepatomas.[23] The cosmetic industry is aware of the problem and is making an effort to lower or remove 1,4-dioxane in cosmetics.[24]

Laneths are used in a variety of cosmetic products at concentrations up to 10%. Thus, a product containing 10% Laneth may contain as much as 3.8% Choleth.[2] The maximum product use concentration of Choleth-24 is 5%.

Acute animal toxicology data available indicate that Laneths are practically nontoxic when in-

gested; undiluted Laneths, equivalent to 38% Choleths, are slightly to severely irritating to rabbits' skin, whereas 10% Laneth solutions, equivalent to 3.8% Choleths, are practically nonirritating to mildly irritating. Undiluted Laneths (38% Choleths) are nonirritating to minimally irritating when instilled into rabbits' eyes (irritancy is reduced if eyes are rinsed). The available animal toxicity data for Choleth correspond well with those for the Laneths. Undiluted Choleth-24 was determined to be slightly toxic when ingested, nonirritating to mildly irritating to rabbits' skin, and practically nonirritating to rabbits' eyes.

In clinical irritation and sensitization tests Laneths-5, -16, and -25 proved to be nonirritating and nonsensitizing at 50% (19% Choleths). Similarly, Choleth-24 (undiluted and in formulation) was found to be nonirritating to mildly irritating and nonsensitizing.

Available test data on phototoxicity and photoallergenicity of Choleth-24 are not in themselves adequate, but clinical experience with it and the Laneths reveals no evidence suggesting that this ingredient is phototoxic or photoallergenic.

CONCLUSION

On the basis of available data, the Panel concludes that Choleth-24 is safe for topical application to humans in the present practices of use and concentration.

ACKNOWLEDGMENT

Mr. Kevin Fisher, Scientific Analyst and writer, prepared the Technical Analysis used by the Expert Panel in developing this report.

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CHOLETH-24

A safety assessment of Choleth-24 was published in 1982 with the conclusion "safe for topical application to humans in the present practices of use and concentration" (Elder 1982).

Studies available since that safety assessment was completed, along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The CIR Expert Panel noted that Choleth-24 may increase the skin penetration of other cosmetic ingredients, and that this should be considered when formulating cosmetic products.

In 1976, Choleth-24 was used in 135 cosmetic products, with the largest single use in hair dyes and colors in the concentration range of >0.1% to 1%. Currently there are uses reported in 191 products, with the largest single use also in hair dyes and colors at a maximum concentration of 0.5% (0.3% after dilution).

Table 7 presents the available use information.

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TABLE 7
Historical and current cosmetic product uses and concentrations for Choleth-24

Product category	1976 use (Elder 1982)	2002 use (FDA 2002)	1976 concentrations (Elder 1982) (%)	2002 concentrations (CTFA 2002) (%)
Bubble baths	1	2	>1–5	—
Eyeliner	14	—	>1–5	0.3
Eye shadow	2	1	>0.1–1	—
Eye lotion	—	1	—	0.3
Mascara	6	—	>0.1–5	0.2
Eye makeup preparations (other)	1	2	>0.1–1	0.3
Perfumes	—	9	—	0.3
Sachets	—	—	—	0.3
Fragrance preparations (other)	—	8	—	—
Hair conditioners	10	9	>0.1–5	0.3–1
Rinses (noncoloring)	—	—	—	0.2
Shampoos (noncoloring)	3	1	>0.1–5	—
Hair tonics, dressings, etc.	1	2	>1–5	—
Hair preparations (other)	—	3	—	—
Hair dyes and colors	71	38	>0.1–1	0.5 (0.3 after dilution)
Blushers	1	—	>0.1–1	—
Face powders	—	—	—	0.2
Foundations	—	19	—	0.2–0.3
Leg and body paints	1	—	>1–5	—
Makeup bases	1	—	>0.1–1	0.5
Makeup (other)	1	2	>1–5	0.2–0.5
Cuticle softeners	—	—	—	0.3
Bath soaps and detergents	—	—	—	0.002–0.7
Aftershave lotion	1	7	>1–5	0.3
Skin-cleansing creams, lotions, liquids, and pads	4	—	>0.1–1	0.3
Face and neck skin care preparations	5*	4	≤0.1–1*	0.4
Body and hand skin care preparations		28		0.1–0.7
Foot powders and sprays	—	1	—	0.3
Moisturizers	2	28	0.1–1	0.008–1.3
Night skin care preparations	2	6	>0.1–1	0.2–0.3
Paste masks (mud packs)	—	1	—	0.3
Skin fresheners	2	2	>0.1–5	—
Skin care preparations (other)	8	11	>0.1–1	0.1–0.3
Suntan gels, creams, and liquids	—	3	—	0.3
Indoor tanning preparations	—	2	—	—
Suntan preparations (other)	—	1	—	—
Total uses/ranges for Choleth-24	**135**	**191**	**≤0.1–5**	**0.002–1.3**

*This category was combined when the original safety assessment was performed and is now two separate categories.

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DIBUTYL PHTHALATE, DIETHYL PHTHALATE, AND DIMETHYL PHTHALATE

A safety assessment of Dibutyl Phthalate (DBP), Diethyl Phthalate (DEP), and Dimethyl Phthalate (DMP) was published in 1985 with the conclusion that these ingredients "are safe for topical application in the present practices of use and concentrations in cosmetics" (Elder 1985). Since then many additional studies have appeared in the scientific literature. These studies, along with the updated information in Table 8 regarding uses and use concentrations, were considered by the CIR Expert Panel. Based on its consideration of the data discussed below, the Panel decided not to reopen this safety assessment.

DBP, DEP, and DMP are phthalate diesters that are used in cosmetics as plasticizers, solvents and fragrance ingredients in a wide variety of cosmetic product types. DEP is also used as a denaturant. DBP is found primarily in nail care products (at concentrations up to 15%) and in some hair care formulations (up to 0.1%). DEP is found in certain bath preparations, fragrance products, deodorants, lotions, and other skin care products. The highest reported concentration of use of DEP is 11% in perfumes. DMP is an ingredient in some hair care products, including aerosol fixatives. The reported maximum concentration of use of DMP in cosmetics is 2% in aerosol hair sprays. Table 8 provides the frequency and concentration of use as a function of product type.

Recent studies document that DBP, DEP, and DMP all absorb readily through the skin and through the gastrointestinal (GI) tract. Once absorbed, most short-chain phthalate diesters are hydrolyzed to the corresponding monoester and alcohol. The phthalates and their metabolites distribute to most tissues, and cross the placenta, but they do not accumulate in any specific tissue type. Phthalates are quickly eliminated in the urine, usually as the corresponding monoester or its glucuronide conjugate. However, humans and primates metabolize longer-chain diester phthalates (e.g., DEHP) into the glucuronide-conjugated monoester forms to a much larger extent than do rats. Also, rats excrete three to four times more free unconjugated MBP than do hamsters given similar doses of DBP or MBP, possibly due to greater testicular β-glucuronidase activity in rats than in hamsters. Phthalates undergo some enterohepatic cycling, and some phthalate is eliminated in the feces.

New data on acute and short-term toxicity were consistent with previously available data.

In a NTP study, DBP, DEP, and DMP were not found to be dermal irritants or sensitizers, confirming previous data using human and animal subjects.

Although previous data had identified that orally administered (in feed or by gavage) DBP and its metabolite MBP have reproductive and developmental effects in rodents, with impaired male development being the most sensitive effect, newly available data provided additional demonstration of such effects.

When pregnant rats and mice were exposed to 1.0% DBP in powdered feed throughout gestation, the pregnancy outcome showed reductions in fertility, number of pups per litter, number of live pups, and body weights of pups. Adult male rats exposed to 1.0% DBP showed signs of liver and kidney toxicity and reduced weights of the prostate, testes, and seminal vesicles. Pregnant rats exposed to 2% DBP in feed throughout pregnancy had a higher incidence of preimplantation loss and resorptions, and no male pups were born alive. Exposure to 1% or 2% DBP in feed only during the latter half of gestation did not show the preimplantation loss and resorption rate seen in rats exposed throughout pregnancy. However, the increased survivability of these fetuses allowed the morphological defects of developing fetuses to be observed. These defects included reduced body weights in both sexes at 2% DBP, reduced anogenital distance and undescended testes in male fetuses at 1% and 2% DBP, and increased incidence of cleft palate and fused sternebrae. Adverse fetal effects were not seen in this study in a 0.5% DBP feed group, or at 331 mg/kg/day, based on average food consumption.

Oral intubation (gavage) of DBP in rats during gestation produced similar effects to those seen in the feeding studies described above. Pregnant rats given oral doses of approximately 0.63 to 0.75 g/kg/day and higher on certain gestation days produced litters with higher incidences of fetal toxicity and malformations. Exposure to DBP on gestation days 7 through 9 or on days 13 through 15 results in increased incidence of skeletal malformations such as cleft palate, fused sternebrae, and vertebral anomalies, as well as dilatation of the renal pelvis and undescended testes. However, exposure to DBP on gestation days 10 through 12 did not produce these effects, suggesting that DBP teratogenicity may be age dependent. Prenatal exposure to MBP appears to produce fetotoxicity and teratogenicity similar to DBP, following the same patterns of age-dependent sensitivity and dose efficacy. This supports the proposal that it is the monoester metabolite that produces the developmental toxicity of DBP and other phthalates.

DEP fed to mice at concentrations up to 2.5% (calculated to be 3.64 g/kg/day) in a continuous breeding protocol produced no effects of DEP on fertility or pregnancy outcome in the F_0 generation. F_1 male mice of the 2.5% DEP group had enlarged prostates and reduced sperm counts, but sperm motility and morphology were not affected. The F_2 generation showed no treatment-related differences between DEP and control groups. Pregnant rats fed up to 5.0% DEP mixed in feed on gestation days 6 through 15 produced no treatment-related alterations in fetal viability or development.

Repeated dermal application of 2 ml/kg up to 50% DEP to pregnant rabbits on gestation days 6 through 18 did not produce maternal or fetal toxicity or affect fetal development.

DMP was not fetotoxic or teratogenic when administered dermally (in rats) or orally (in rats and mice) during gestation.