Safety Assessment of PEG Diesters as Used in Cosmetics

Status:	Re-Review for Panel Review
Release Date:	November 14, 2014
Panel Meeting Date:	December 8-9, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: November 14, 2014

Subject: Safety Assessment of PEG Diesters As Used In Cosmetics

Attached is the re-review of PEG distearates, which is being proposed to be combined with other similar ingredients to create a group of PEG diesters. [*PEGDie_122014_rep*] This report combines the PEG distearates (1999) [*PEGDie_122014_Data1*], the PEG dilaurates (2000) [*PEGDie_122014_Data2*], and other un-reviewed PEG diesters that are used in cosmetics. The Panel concluded that PEG distearates were safe as used and that the PEG dilaurates were safe up to 25%. PEG-4 diisononanoate was reviewed with pelargonic acid-related ingredients in 2011with a safe as used conclusion.

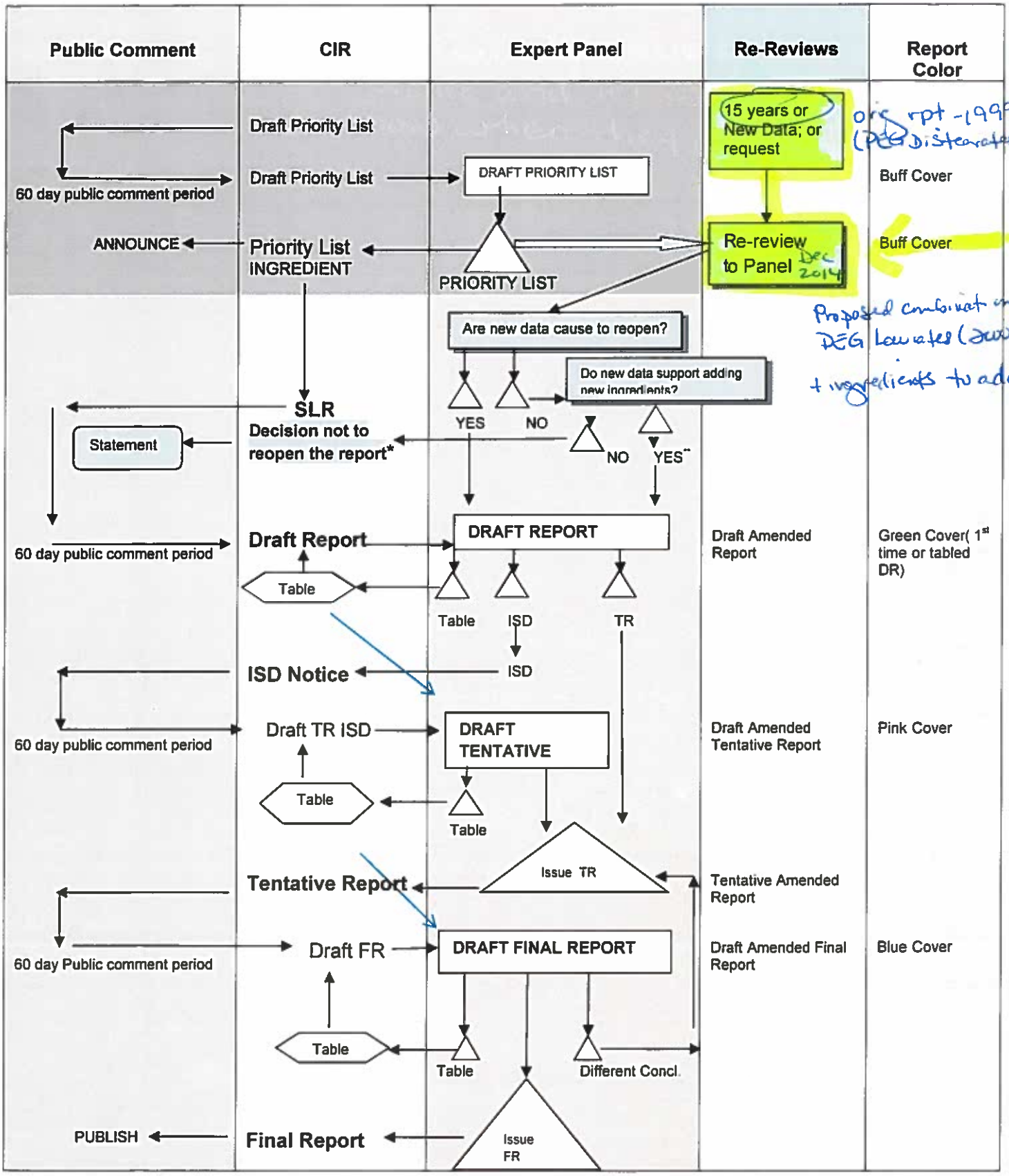
Concentration of use data, submitted by industry, have been added to the report. [*PEGDie_122014_Data3; PEGDie_122014_Data4*] There were little new data found in the literature; no additional data were submitted. In the previous safety assessments, the Panel relied on data on related ingredients to assess the safety. For example, the Panel unanimously concluded that PEGs-2, -3, -4, -6, -8, -9, -12, -20, -32, -75, -120, -150, and -175 distearates were safe as used (with caveats) using information from four CIR reports (PEGs, PEG stearates, stearic acid, and steareths) as well as information summarized from a fifth CIR report on the developmental and reproductive toxicity of ethylene glycol and its ethers.

The Panel is to examine the new data and decide whether to affirm the conclusion or to reopen this safety assessment to change the conclusion. The Panel is also to review the additional ingredients and decide if any or all belong in this group of PG diesters. If so, then the Panel is to open the re-review to add these ingredients.

PEG Diesters

Dec 2014

SAFETY ASSESSMENT FLOW CHART



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

Report History for PEG Diesters

1999 – PEG Stearate report published with a safe as used conclusion.

2000 – PEG Laurate report published with a safe up to 25% conclusion.

2011 – PEG-4 Diisononanoate was safe as used in a report on pelargonic acid and related ingredients.

2013 – PEG Stearates added to re-review list for 2014.

December, 2014 – Panel examines re-review document which includes the addition of PEG Laurates and other PEG Diesters (for a total of 55).

PEG Diesters Data Profile for December, 2014. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
PEG-2 distearate			N															
PEG-3 distearate			N															
PEG-4 distearate			N															
PEG-6 distearate			N															
PEG-8 distearate			N	O														
PEG-9 distearate																		
PEG-12 distearate			N															
PEG-20 distearate				O														
PEG-32 distearate																		
PEG-40 distearate																		
PEG-75 distearate																		
PEG-120 distearate			N															
PEG-150 distearate			N															
PEG-175 distearate			N															
PEG-190 distearate																		
PEG-250 distearate			N															
PEG-150 dibehenate																		
PEG-3 dicaprylate/caprate																		
PEG-4 dicocoate																		
PEG-8 dicocoate			N															
PEG-4 diheptanoate			N	N		N	N		N	N	N		N			N		
PEG-2 diisononanoate			N															
PEG-2 diisostearate																		
PEG-3 diisostearate																		
PEG-4 diisostearate																		
PEG-6 diisostearate			N															
PEG-8 diisostearate			N															
PEG-12 diisostearate			N															
PEG-90 diisostearate			N															
PEG-175 diisostearate			N															
PEG-2 dilaurate																		
PEG-4 dilaurate			N				O											
PEG-6 dilaurate																		
PEG-8 dilaurate			N															
PEG-12 dilaurate																		
PEG-16 dilaurate																		
PEG-20 dilaurate																		
PEG-32 dilaurate																		
PEG-75 dilaurate																		
PEG-150 dilaurate																		
PEG-2 dioleate																		
PEG-3 dioleate																		

PEG Diesters Data Profile for December, 2014. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
PEG-4 dioleate																		
PEG-6 dioleate																		
PEG-8 dioleate			N															
PEG-10 dioleate																		
PEG-12 Dioleate			N															
PEG-20 Dioleate																		
PEG-32 Dioleate																		
PEG-75 Dioleate																		
PEG-150 Dioleate																		
PEG-3 Dipalmitate																		
PEG-8 Ditallate																		
PEG-12 Ditallate																		

N = new data

O = data from old report

Search Strategy

SciFinder – Ingredient names and CAS Nos. **–**

52668-97-0 - 2 hits, not useful.

9005-08-7 - 1265 hits, Culled by general terms (adverse effect, biological study, properties) – 699 hits. Removed patents – 89 hits. 4 might be useful.

142-20-1 – 4 hits – 0 useful.

109-34-2 – 5 hits – 0 useful

109-30-8 – 78 hits – 0 useful

70729-68-9 – 99 hits; removed patents – 5 hits. 1 useful.

9009-37-4 – 12 hits. 0 useful.

9005-07-06 – 612 hits, removed patents, 51 hits. 2 useful.

9005-02-1 – 473 hits, removed patents, 53 hits. 2 useful

134141-38-1 – 5 hits. 0 useful.

52668-97-0 – 2 hits. 0 useful.

32628-06-1 – 52 hits, removed patents, 12 hits.0 useful.

6281-04-5 – 21 hits. 0 useful.

7 papers ordered after removal of duplicates and further examination.

ECHA – CAS Nos. – No hits.

HPVIS – CAS Nos. – Data on PEG-4 diheptanoate (some duplicate information).

Historical Minutes for PEG Diesters

PEG DISTEARATES

March, 1995

PEG Distearates

INSUFFICIENT DATA ANNOUNCEMENT

(1) Concentration of use of a prototypical high and low molecular weight compound

(2) Chemical and physical properties

(3) 28-day dermal toxicity on PEG-2 Distearate

(4) Dermal irritation and sensitization on PEG-2 Distearate

(5) Ocular irritation, if available

(6) Two genotoxicity tests, one in a mammalian system, on PEG-2 Distearate; if the results are positive, then a dermal carcinogenesis study using NTP methods may be needed

(7) A review of the literature addressing the teratogenic potential of ethylene glycol and ethylene glycol ethers will be conducted and included in the discussion section of the report. Teratogenicity testing may be required.

May, 1995

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -75, -120, -150, and -175 Distearates

The Panel voted unanimously in favor of issuing an Insufficient Data Announcement with the following data requests:

(1) Concentrations of use of one prototypical high and one prototypical low molecular weight PEG Distearate

(2) Chemical and physical properties

(3) 28-day dermal toxicity on PEG-2 Distearate

(4) Dermal irritation and sensitization data on PEG-2 Distearate at concentrations of use

(5) Ocular irritation, if available

(6) Two genotoxicity tests, one in a mammalian system, on PEG-2 Distearate; if the results are positive, then a dermal carcinogenicity study using NTP methods may be needed

(7) A review of literature addressing the teratogenic potential of ethylene glycol and ethylene glycol ethers will be conducted and included in the report.

Depending on the results of a review of that data, teratogenicity testing may be required.

December, 1995

PEGs-2, -3, -4, -8, -9, -12, -20, -32, -75, -120, -150, and -175 Distearate

Dr. Schroeter noted that an Insufficient Data Announcement on these ingredients was issued at the May 22-23, 1995 Panel meeting. The data requests included in this announcement were as follows:

(1) Concentration of use on one prototypical high and one prototypical low molecular weight PEG Distearate

(2) Chemical and physical properties

(3) 28-day dermal toxicity on PEG-2 Distearate

(4) Dermal irritation and sensitization on PEG-2 Distearate at concentration of use

(5) Ocular irritation, if available

(6) Two genotoxicity tests, one in a mammalian system, on PEG-2 Distearate; if the results are positive, then a dermal carcinogenesis study using NTP methods may be needed

(7) A review of literature addressing teratogenic potential of ethylene glycol and ethylene glycol ethers will be conducted and included in the report.

Depending on the review of that data, teratogenicity testing may be required

He noted that items 1 through 6 were not received in response to the Insufficient Data Announcement that was issued, and that these data are still needed in order for the Panel to complete its safety assessment. Development of the CIR review on ethylene glycol teratogenicity is ongoing.

The Panel voted unanimously in favor of tabling the CIR report on this group of ingredients, pending the teratogenicity review on ethylene glycol.

March, 1996

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32 -75, -120, -150, and -175 Distearate

Dr. Schroeter stated that there has been no response to the Insufficient Data Announcement on these ingredients that was issued on May 23, 1995. However, he noted that data from the CIR report on PEG Stearates have been incorporated into the present report, thereby eliminating the need for all of the data requested in the Insufficient Data Announcement. Thus, Dr. Schroeter's Team concluded that the PEG Distearates are safe as used.

Dr. Belsito noted that information from the following three CIR reports should be incorporated into the report on PEG Distearates: PEGs, PEG Stearates, Stearic Acid, and Steareths.

Dr. Bergfeld confirmed that a summary of data from the CIR report on the developmental and reproductive toxicity of ethylene glycol and its ethers will be incorporated into the present report.

Dr. Schroeter said that he would like to have an opportunity to review the report on PEG Distearates before it is announced as a Tentative Report, considering that this report will eventually contain data from the following four CIR reports: PEGs, PEG Stearates, Stearic Acid, and Steareths. He suggested that some or all of the Panel members review this document after studies from earlier CIR Reports have been incorporated. Dr. Schroeter stressed the need to ensure that other members of the Panel are comfortable with the fact that the data incorporated will also be used to assess the safety of the low molecular weight PEG-2 Distearate, particularly in the area of genotoxicity.

Dr. Bergfeld reminded the Panel that, as discussed earlier, the report discussion may be used to address any issues, such as genotoxicity and impurities.

Dr. Schroeter reiterated that whether or not the Panel agrees that the data from the four CIR reports are sufficient for evaluating the safety of all of the PEG Distearates included in this review should be determined.

The Panel unanimously concluded that PEGs -2, -3, -4, -6, -8, -9, -12, -20, -32, -75, -120, -150, and -175 Distearate are safe as used (with caveats), using information from four CIR reports (PEGs, PEG Stearates, Stearic Acid, and Steareths) as well as information summarized from a fifth CIR report on the developmental and reproductive toxicity of Ethylene Glycol and its ethers. It was also agreed that the report discussion will include the pivotal points that led to this conclusion, as well as any other concerns that should be addressed.

Dr. McEwen confirmed with the Panel that the following caveats are to be incorporated into the report discussion: (1) Don't use on damaged skin, (2) Impurities, particularly ethylene oxide and 1,4-dioxane, should be maintained at sufficiently low levels to minimize their genotoxic potential, and (3) In the absence of inhalation toxicity data, there is no reason for concern about toxicity relative to this route of exposure because of the large molecular size of these chemicals.

Dr. Bergfeld noted that there are a number of documents (approximately 8) with the same issues as those outlined for the PEG Distearates that will have to be returned to the Panel. She said that, at this point, the degree of review of these documents that is needed should be considered.

Dr. Andersen said that a summary of the Polyethylene Glycol data and data from reports on the relevant fatty acids will be added to the following reports that are being reviewed today: Ceteths, Oleths, PEG Cocamines, PEG Distearates, and the PEG Lanolins. Additionally, for PEG Distearates, data on PEG Stearates and the Steareths will be incorporated in addition to the Polyethylene Glycol data and data on Stearic Acid.

Dr. Bergfeld agreed to review the following documents prior to their announcement as Tentative Reports: Ceteths, Oleths, PEG Cocamines, and PEG Lanolins [The Panel's discussion on PEG Lanolins is included in the next section of the minutes]. However, she requested that the full Panel review the document on PEG Distearates prior to Tentative Report announcement, given the fact that data from four different CIR safety assessments will be incorporated.

Dr. Andersen noted that these Tentative Reports will not be scheduled for review at the June 3-4, 1996 Panel meeting. Therefore, if the issuance of these reports is delayed, pending reviews by Dr. Bergfeld and the full Panel, there still will be an adequate amount of time for the receipt of comments prior to the September 19-20, 1996 Panel meeting

Dr. Bergfeld clarified that the report on PEG Distearates had not been tabled by the Panel.

Dr. Andersen noted that the Panel concluded that the PEG Distearates are safe as used. However, the document will be further reviewed (editorial review) by the Panel prior to public announcement.

September, 1996

PEG -2, -3, -4, -6, -8, -9, -12, -20, -32,

-50, -75, -120, -150, and -175 Distearate

The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: PEGs -2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are safe for use in cosmetic formulations under the present practices of use.

PEG DILAURATES

June, 1997

PEGs -2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEGs -2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE

Dr. Andersen noted that, normally, an informal data request is issued during the initial review of an ingredient report. However, in this case, it was determined in Teams that the data included in the Draft Report are sufficient for arriving at a conclusion on the safety of these ingredients.

Dr. Belsito noted that current concentration of use data are not available; however, the 1984 data indicated ingredient use at concentrations up to 25%. He also noted that the results of a chronic oral toxicity study on 25% PEG-20 Laurate are included in the report text. Based on the results of this study, the Belsito Team proposed a conclusion of safe for use in cosmetics at concentrations up to 25% for the PEGs Dilaurate ingredient family.

Dr. Schroeter questioned the proposed 25% concentration limit, and suggested a conclusion of safe as used for this ingredient family. He noted that 25% is at the high end of the use concentration range, and that it is not necessary to specify this high concentration in the report conclusion.

Ms. Fise reiterated that the 25% concentration limit is based on 1984 concentration of use data, old data.

Dr. Belsito noted that data on 25% aqueous PEGs Stearate as well as a chronic oral toxicity study on PEGs Dilaurate at concentrations up to 25% are included in the Draft Report.

The Panel unanimously concluded that PEGs -2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEGs -2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and

-200 Laurate; and PEG-2 Laurate SE are safe as used at concentrations up to 25%, and voted in favor of issuing a Tentative Report.

December, 1997

PEGs -2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEGs -2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE

The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: On the basis of the available data, the CIR Expert Panel concludes that PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE are safe for use in cosmetics at concentrations up to 25%.

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INTRODUCTION

This is a re-review of the safety assessment of polyethylene glycol (PEG) diesters as used in cosmetics. These ingredients are diesters of various fatty acids with the common core of the PEG moiety. These ingredients mostly function in cosmetics as surfactants (Table 1).

In 1999, the Cosmetic Ingredient Review (CIR) Expert Panel published a safety assessment of PEG distearates with the conclusion of safe as used (Table 2).[1] Because of they are similarly structured fatty acid diesters with a PEG core, PEG dilaurates and other similar ingredients are included in this safety assessment. In 2000, a safety assessment of PEG dilaurates was published with the conclusion of safe for use in cosmetics at concentrations up to 25%.[2] In 2011, a safety assessment of pelargonic acid-related ingredients, that included PEG-2 diisononanoate, was published with a conclusion of safe in the present practices of use and concentration.[3] Because there were little data available on the individual ingredients in these safety assessments, the Panel relied on read across and information on the moieties of these ingredients. Summaries of the reports on PEG distearate and PEG dilaurates are provided below. PEG-50 distearate, which was included in the original safety assessment, is not currently listed as a cosmetic ingredient.

Because of similarities in chemical structure and cosmetic function, the following PEG diesters have been added to this safety assessment:

PEG-40 distearate
PEG-190 distearate
PEG-250 distearate
PEG-150 dibehenate
PEG-3 dicaprylate/caprate
PEG-4 dicocoate
PEG-8 dicocoate
PEG-4 diheptanoate
PEG-2 diisostearate
PEG-3 diisostearate
PEG-4 diisostearate
PEG-6 diisostearate
PEG-8 diisostearate
PEG-12 diisostearate
PEG-90 diisostearate
PEG-175 diisostearate
PEG-2 dioleate
PEG-3 dioleate
PEG-4 dioleate
PEG-6 dioleate
PEG-8 dioleate
PEG-10 dioleate
PEG-12 dioleate
PEG-20 dioleate
PEG-32 dioleate
PEG-75 dioleate
PEG-150 dioleate
PEG-3 dipalmitate
PEG-8 ditallate
PEG-12 ditallate

CIR has conducted safety assessments of the acids and related moieties of these ingredients. These are also provided in Table 2. The Panel concluded that coconut acid, isostearic acid, oleic acid, lauric acid, stearic acid, PEGs (just the polyether chain without the endcap esters), PEG stearates (PEG monoesters), stearates, and tall oil acid were safe as used.[4-16] The Panel concluded that steareths (PEG ethers) were safe as used when formulated to be nonirritating.[17-19]

SUMMARIES OF ORIGINAL REPORTS

PEG Distearates

PEG-2,-3,-4,-6,-8,-9,-12,-20,-32,-50,-75,-120,-150,and -175 Distearate are the polyethylene glycol diesters of Stearic Acid.[1] These ingredients are surfactants that function as emulsifying, cleansing, and solubilizing agents in cosmetics. Product formulation data submitted to the Food and Drug Administration (FDA) indicate that PEG-2, -3, -4, -6,-8, -12, -50, and -150 Distearate were in use, and that they were used in 283 cosmetic formulations.

Because few data on the PEGs Distearate regarding metabolism, toxicity, mutagenicity, carcinogenicity, and clinical safety were available, this review presented data on the PEGs, Stearic Acid, Steareths, and the PEGs Stearate separately, as these data were considered applicable to the safety evaluation of the PEGs Distearate.

PEG Distearate absorption and metabolism data were not available. PEG absorption is related to molecular weight. Lower molecular weight PEGs are readily absorbed through damaged skin. Oral and intravenous studies on PEGs indicate that these substances are excreted, unchanged, in the urine and feces. In general, fatty acids (such as Stearic Acid) are readily absorbed and distributed to the tissues in humans. Fatty acids can traverse the placental barrier.

Toxicity data for the PEGs Distearate were not available. The PEGS Stearate, and Steareths had low oral toxicity in acute, short-term, subchronic and chronic studies. PEGs in general have a low oral and dermal toxicity; the larger molecular weight PEGs appear to be less toxic than the smaller PEGs in oral studies. The acute toxicity of cosmetic formulations containing up to 13% Stearic Acid was low. In subchronic and chronic feeding studies using rats the effects were more severe.

PEG Stearates were slightly irritating at undiluted concentrations in test animals. PEGs were nonirritating to the skin of rabbits and guinea pigs, and PEG-75 was not a sensitizer. Stearic Acid irritation ranged from moderate to no

reaction. Cosmetic product formulations containing 1.0% Stearic Acid were weak, grade I sensitizers. Primary irritation and sensitization studies involving Stearic Acid and the PEGs Stearate were negative. Minimal ocular irritation occurred in tests with the PEGs, Stearic Acid, Steareths, and PEGs Stearate.

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, it was considered unlikely that the PEGs Distearate would cause reproductive or developmental effects based on their structural characteristics. In subchronic and chronic feed studies, PEG-6 [through]*32 and PEG-75 did not induce adverse reproductive effects in rats. In a multigenerational study lasting 2 years, feed containing l0-20% PEG-8 Stearate or PEG-40 Stearate was fed to rats; the rats fed the diet had decreased offspring survival time, reproductive performance, and lactation efficiency, as well as increased offspring mortality. Neither PEG-8 Stearate nor PEG-40 Stearate at a dietary concentration of 5% affected reproductive success.*

In mutagenicity studies, PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test. At concentrations up to 150 g/l, PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay. Stearic Acid was not mutagenic in the Ames test. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to rodents. A low incidence of carcinomas, sarcomas, and lymphomas was evident in mice receiving multiple subcutaneous injections of Stearic Acid.

In clinical studies, PEG-8 was a mild sensitizer and irritant. Contact dermatitis and systemic toxicity in burn patients were attributed to a PEG-based topical ointment. The Steareths, PEGs Stearate, and Stearic Acid were not irritants, sensitizers, or phototoxins. Formulations containing Stearic Acid were not photosensitizing.

PEG Dilaurates

The PEGs Dilaurate, PEGs Laurate, and PEG-2 Laurate SE are PEG diesters or esters of lauric acid that function as surfactants in cosmetic formulations.[2] *In 1997, PEG-8 Dilaurate and PEG-12 Dilaurate were used in 40 cosmetic formulations, and PEG-2, -4, -8, -10, -15, and -200 Laurate were used in 20 formulations. The remaining ingredients from this family had no reports of use. In 1984, data submitted to the FDA indicated that the PEGs Dilaurate and PEGs Laurate were used at concentrations up to 25%.*

The CIR Expert Panel has previously reviewed the safety in cosmetics of the PEGs Stearate, PEGs Distearate, PEGs, Laureths, and Lauric Acid. Based on the similarity in chemical structures, data from those evaluations have been used as a further basis for the safety assessment of the PEGs Dilaurate and PEGs Laurate in cosmetics.

These polyoxyethylene ester surfactants and emulsifiers are produced by the ethoxylation of fatty acids during uncatalyzed or alkali-catalyzed reactions. PEG-2 Laurate has been produced by the interesterification of coconut oil with diethylene glycol. PEG-n Laurate could contain unspecified amounts of the lauric acid diester of PEG and unreacted PEG. PEG-6 may contain small, unquantified amounts of monomer and dimers, and samples PEG-32 and PEG-75 contained peroxides as a result of autoxidation. In general, ethoxylated surfactants can contain 1,4-dioxane, a by-product of ethoxylation, which is then removed during purification of the finished products. Traces of the reactants, stearic acid, ethylene oxide, and the catalysts used could remain in the finished product.

Data on the absorption, metabolism, distribution, and excretion of the PEGs Dilaurate and PEGs Laurate were not available. PEG-40 Stearate was hydrolyzed in vitro by pancreatic lipase. In metabolism studies with rats, rabbits, dogs, and humans, the lower-molecular-weight PEGs were absorbed by the digestive tract and excreted in the urine and feces. The PEGs were readily absorbed through damaged skin.

Fatty acids such as Lauric Acid are absorbed, digested, and transported in animals and humans. During labeling studies, radioactivity was found in various tissues, blood, and lymph after oral, IV, IP, and intraduodenal administration of labelled fatty acids. The fatty acids can undergo ß-oxidation to yield acetyl-CoA. Placental transfer of the fatty acids has been observed. Lauric Acid is transported via the lymph and portal systems; fatty acids are typically transported esterified to glycerol in chylomicrons and very-low-density lipoproteins.

The acute oral LD_{50} of PEG-12 Laurate was >25 g/kg in Harlan mice. In the same study, the IV LD_{50} was 500 mg/kg. During short-term feeding studies using chicks, concentrations of up to 2% PEG-4 or-8 Laurate did not cause adverse effects. Rats fed a diet containing 15.9 g/kg/day of 25% PEG-20 Laurate had diarrhea, inflammation of the anal region, and blood clots in the anorectal region after 59 days of treatment. In a 70-day study, rats given 5% to 25% PEG-20 Laurate had diarrhea and inflammation of the anal region. The ingredient was irritating to the gastrointestinal tract, but not necrotizing, and monocyte/macrophage hyperplasia and splenic giant cells were noted more frequently in rats of the treated group than rats of the control group. In a chronic oral toxicity study, nine rats were fed 6% PEG-8 Dilaurate for 505 days. Four of the rats in each of the treatment and control groups died. Of the rats given PEG-8 Dilaurate, one had cystic spots on the liver, one had hemorrhagic lungs, and one had a large fibrosarcoma. In microscopic examinations, three rats had focal parenchymal hepatitis. Of the rats of the control group, four had hemorrhagic and congested lungs, one had hypertrophied testes, one had a concretion in the urinary bladder, two had cystic kidneys, and two had hepatic parasites. In microscopic examinations, one control rat had adrenal cortical hyperplasia, two had chronic interstitial nephritis of the kidneys, two had splenic lymphoid hyperplasia, one had focal parenchymal hepatitis, and one had hepatic vacuolization. During another feeding study, rats fed up to 25% PEG-20 Laurate for 2 years had hepatic cysts, cecal enlargement, slight gastric mucosal hyperplasia, and slight squamous epithelial hyperplasia. PEG-12 Laurate at a concentration of 1% did not cause ocular irritation in rabbits.

The IV LD_{50} values in Harlan mice for PEG-8 and -20 Distearate were 365 mg/kg and 220 mg/kg, respectively. The oral LD_{50} values of PEG-2-150 Stearate ranged from >10 g/kg to 32 g/kg in rats. The IP LD_{50} of PEG-8 Stearate in rats was >9 ml/kg. No signs of toxicity were observed when rats were given IP injections of 2.5 g/kg PEG-50 or -100 Stearate. A hair cream containing 1.5% PEG-6 Stearate had an oral LD_{50} of >34.6 g/kg. The acute dermal LD_{50} of 15% PEG-8 Stearate in rabbits was >10 ml/kg; the only effect noted was erythema at the application site at 24 hours. The PEGs Stearate caused only slight skin irritation and minimal ocular irritation when tested at concentrations of 100% in animals. PEG-8, -40, and -100 Stearate did not cause significant changes in growth mortality rates, microscopic observations, or hematological values during long-term feeding studies. In clinical studies, the PEGs Stearate were not irritating or sensitizing when tested at concentrations of25%. In addition, they did not cause photosensitization. PEG-8 and -40 Stearate did not cause reproductive or developmental effects, and were noncarcinogenic.

In acute toxicity studies, the PEGs had low oral and dermal toxicity. The PEGs were not irritating to the skin of rabbits or guinea pigs, and minimally irritating to the skin of humans. They did not cause sensitization in animal or human studies using intact skin, but sensitization and nephrotoxicity were observed in bum patients that were treated with a PEG-based cream. PEG was determined to be the causative agent in both animal and human studies. In ocular irritation studies, the PEGs caused mild, transient ocular irritation in rabbits. Cosmetic product formulations containing up to 13% Lauric Acid did not cause primary or cumulative irritation and did not cause sensitization.

The available data indicated that the PEGs were not mutagenic or carcinogenic.

A product formulation containing 5% Lauric Acid was nontoxic to rats during an oral toxicity study. Transient signs of toxicity (mucoid diarrhea, depression, unkempt fur, etc.) were observed when male rats were fed 0.46 to 10 g/kg Lauric Acid. In this study, one rat died; it had congested lungs and kidneys, and advanced autolytic changes. In a subchronic oral toxicity study, rats fed 10% Lauric Acid had no signs of toxicity. Lauric Acid was also noncarcinogenic in animal tests. It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers are reproductive and developmental toxins. The PEGs Dilaurate and PEGs Laurate are diesters and esters of PEG and, as such, are chemically different from PEG alkyl ethers. Hence, they are not expected to cause adverse reproductive or developmental effects.

CHEMISTRY

Definition and Structure

The PEG diesters in this report are the PEG diesters of various acids (eg, stearic acid, lauric acid, oleic acid). The different chain lengths of the PEGs are formed by condensing ethylene oxide and water. The average stoichiometric equivalents of ethylene oxide used correspond to the number in the name (eg, PEG-4 diheptanoate is prepared from 4 stoichiometric equivalents of ethylene oxide, on average).[15]

Physical and Chemical Properties

The PEG distearates have a broad range of properties depending on the degree of polymerization of the PEG segment.[20] The physical forms of these ingredients range from liquids to solids. Solubility is also dependent on the length of the PEG component. Typically, these ingredients are soluble in oil and hydrocarbon solvents when less than 8 ethylene oxide units are present. Solubility in water begins with compounds containing 12-15 ethylene oxide units. Specific gravity and viscosity increase with increasing ethylene oxide content.

For example, PEG-4 diheptanoate was reported to be a clear liquid with a boiling point of > 300˚C, a specific gravity of 0.996, and a vapor pressure of <0.1 mmHg at 37˚C.[21] It is soluble in alcohol, acetone, and most organic solvents.

Method of Manufacture

In general, the PEGs diesters are manufactured by the esterification of an acid with ethylene oxide or with a polyethylene glycol.[20]

Impurities

PEG-150 distearate was reported to contain peroxide concentrations of 1.97 and 1.92 µEq thiosulfate/g glycol.[22] PEGs may contain small amounts of monomer and dimers, as well as peroxides.[23] Peroxide in PEGs is dependent upon the molecular weight of the PEG and its age.[22]

PEGs may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation.[24] 1,4-Dioxane is a known animal carcinogen.[25] Commercial grade triethylene glycol has been found to contain <1 ppm dioxane.[26] The cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations.[15]

PEG-4 diheptanoate was reported to be 88% pure; the rest of the substance consisted of triethylene glycol di-n-heptanoate (6%), mixed ester of tetraethylene glycol with n-heptanoic and 2-methylhexanoic acids (4%), and other mixed esters (2%).[21]

USE

Cosmetic

The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP).[27] Of the ingredients in this safety assessment, PEG-150 distearate was reported to have the highest number of uses at 654 (an increase from 187 in 1996).[1,27] Most of these uses are in bath and personal cleansing products and shampoos. The rest of the ingredients are reported to have 50 or fewer uses (Tables 3, 4). Table 5 lists the ingredients in this report that have no reported uses.

PEG-50 distearate, which was included in the original safety assessment, is not currently listed in the *International Cosmetic Ingredient Dictionary and Handbook*.[28] However, the VCRP has 1 reported use in a cleansing product.[27] In 1996, it was used in 1 cleansing preparation.[1]

A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group.[29] PEG-150 distearate was reported to have the highest concentration of use at up to 33.2% (an increase from 5% in 1995).[1,29] PEG-150 distearate is reported to be used in a rinse-off baby product up to 9.4%, bath products up to 4.5%, and in skin cleansing products up to 33.2%. PEG-4 dilaurate and PEG-8 dilaurate were reported to be used up to 25% in 1984, and are currently used up to 12% and 15%, respectively.[2] The rest of the ingredients were reported to be used at 15% or less (Tables 3, 4, 5).

In some cases, reports of uses were received in the VCRP, but no concentration of use data were available. For example, PEG-120 distearate is reported to be used in 7 formulations, but no use concentration data were available. In other cases, no reported uses were received in the VCRP, but a use concentration was provided in the industry survey. For example, PEG-4 dilaurate was not reported in the VCRP to be in use, but the industry survey indicated that it is used in non-coloring hair formulations at up to 0.72%. It should be presumed that PEG-4 dilaurate is used in at least one cosmetic formulation.

PEG-12 dioleate was reported to be used in pump hair sprays up to 0.024% and PEG-4 dilaurate was reported to be used in a pump spray suntan products at 0.72%, and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.[30-33] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[30,32]

Non-Cosmetic

Several of the PEG diesters may be used as defoaming agents in foods, as indirect food additives in paperboard products, in food contact surfaces, and as additives in animal feed and drinking water (Table 6).[21CFR73.1, 21CFR173.340, 21CFR175.105, 21CFR176.170, 21CFR176.180, 21CFR176.200, 21CFR176.210, 21CFR177.1210, 21CFR177.2260, 21CFR177.2600, 21CFR177.2800, 21CFR573.800, 21CFR573.820]

TOXICOKINETICS

Dermal Penetration Enhancement

Neither PEG-8 dioleate (5% w/w) nor PEG-8 dilaurate (5% w/w) enhanced the dermal penetration of ketoprofen through full-thickness CD-1 nude mouse skin when added to a drug delivery plaster preparation.[34] PEG-12 dioleate (5%) did enhance the dermal penetration of ketoprofen with an enhancement ratio (ER) of 1.54±0.22. The study was conducted using Franz cells; the receptor cell was filled with freshly prepared degassed pH 7.4 phosphate-buffered saline. The samples were taken from the receptor cell and analyzed by high-performance liquid chromatography (HPLC) at 1, 2, 4, 8, and 24 h.

TOXICOLOGICAL STUDIES

Acute Toxicity

Oral – Non-Human

PEG-4 DIHEPTANOATE

The oral LD_{50} of PEG-4 diheptanoate for rats ranged from >2-25 g/kg (Table 7).[21, 35] Clinical signs included labored breathing, belly-to-cage posture, lacrimation, staining of the face, stained and wet perineal area, and weight loss.

Inhalation – Non-Human

PEG-4 DIHEPTANOATE

All the Crl:CD rats (n=6) exposed to vaporized PEG-4 diheptanoate (14.2 mg/L) for 4 h died during the exposures; all rats (n=6) exposed to 13.7 mg/L or less survived.[21] At all concentrations (2.1 – 14.2 mg/L), the clinical signs included salivation, red nasal discharge, and irregular respiration during the exposure period. The rats recovered quickly during the recovery period. Lethargy was observed starting at a concentration of 12.7 mg/L or greater. Rats exposed to 13.7 mg/L showed moderate weight loss (approximately 10% of initial body weight) the first 3 to 4 days post-exposure. The rats with weight loss also presented an unthrifty appearance with staining of the perineal area prominent during the 1st week of the 14-day recovery period. The test material was vaporized by applying heat and not aerosolized.

Repeated Dose Toxicity

Oral – Non-Human

PEG-4 DIHEPTANOATE

There were no adverse effects observed when PEG-4 diheptanoate (1 g/kg in corn oil) was administered by gavage to Crl:CD rats (10/sex) for 28 consecutive days.[21] Pathologic examinations at the end of the test period and after the 14-day recovery period were unremarkable.

Inhalation – Non-Human

PEG-4 DIHEPTANOATE

In the repeated inhalation exposure of PEG-4 diheptanoate (1.0 mg/L) for 6 h/day, 5 days/week for 4 weeks, clinical signs for Crl:CD rats (n=10) were mild salivation, reduced response to auditory stimulation, and shallow and rapid respiration sporadically during the exposure periods.[21] The clinical signs were absent when the rats were not being exposed and during the 14-day recovery period. A trace of lung noise and brown staining of the nose were observed in 1 of the treated rats during recovery. Body weight changes were similar to the controls. Gross pathologic evaluation was unremarkable. Histopathologic examination of tissues found no lesions attributable to the test substance. The test material was vaporized by applying heat and not aerosolized.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

New data on the reproductive and developmental toxicity of PEG diesters were not found in the published literature nor were unpublished data provided.

GENOTOXICITY

PEG-4 DIHEPTANOATE

PEG-4 diheptanoate was not mutagenic in a reverse mutation assay up to 10 000 µg/plate using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 or in a mammalian cell gene mutation assay using Chinese hamster ovary cells up to 23.9 mM (Table 8).[35]

CARCINOGENICITY

New data on the carcinogenicity of PEG diesters were not found in the published literature nor were unpublished data provided.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

PEG-4 diheptanoate (100%; 0.5 mL) caused slight (1 of 6), mild (3 of 6), or no (2 of 6) erythema to the skin of New Zealand White rabbits (n=6) when administered to the skin for 24 h.[21] At the removal of the test material, there was no edema observed on any of the rabbits. At 24 h after removal, there was little change in the erythema responses and edema (moderate in 1 rabbit; mild in 2 rabbits, and absent in 3 rabbits) was observed.

There was no skin irritation observed in a preliminary study using male BC/DHA guinea pigs (n=3) treated with PEG-4 diheptanoate (5% or 25%; 0.05 mL in dimethyl phthalate).[21] At a concentration of 50%, mild irritation in 1 guinea pig was observed, and at 100% there was mild irritation on all 3 guinea pigs.

Ocular

There were no lasting reactions observed when PEG-4 diheptanoate (100%; 0.1 mL) was administered in the conjunctival sac of New Zealand White rabbits (n=2).[21] The cornea, iris, and conjunctiva of 1 rabbit (the treated eye of this rabbit remained unwashed following administration) showed no adverse effects. The other rabbit eye (the treated eye of this rabbit was washed with copious amounts of water 20 seconds after administration) showed slight conjunctival swelling which lasted for 4 h. The swelling was resolved at 24 h. No changes in the corneal or iritic tissues were observed.

Sensitization

Dermal – Non-Human

In a dermal sensitization study using male BC/DHA guinea pigs (n=10), PEG-4 diheptanoate (5% or 25%; 0.05 mL in dimethyl phthalate) was not sensitizing when challenged at 5% or 50%.[21] The test substance was administered to the shaved skin of the shoulder of the guinea pigs followed 2 days later by an injection of dimethyl phthalate (1%; 0.1 mL). Three more injections, 1 week apart, were administered to complete the induction phase. After a 13-day rest period, the challenge was administered as a topical administration of PEG-4 diheptanoate (5% or 50% in dimethyl phthalate; 0.05 mL) to

the same shaven shoulder. The control consisted of a group of naïve guinea pigs (n=10) that were administered the challenge. Test sites were evaluated for reactions at 24 and 48 h after administration of the challenge.

SUMMARY

This is a safety assessment of PEG diesters as used in cosmetics. These ingredients are diesters of various fatty acids with the common core of the PEG moiety. These ingredients mostly function in cosmetics as surfactants.

In previous safety assessments, it was concluded that several PEG distearates were safe as used in cosmetics and several PEG dilaurates were safe up to 25%. PEG-2 diisononanoate was also found to be safe as used.

Of the ingredients in this safety assessment, PEG-150 distearate was reported to have the highest number of uses at 654 (an increase from 187 in 1996). Most of these uses are in bath and personal cleansing products and shampoos. The rest of the ingredients are reported to have 50 or fewer uses. PEG-150 distearate was reported to have the highest concentration of use at up to 33.2% (an increase from 5% in 1995). PEG-150 distearate is reported to be used in a rinse-off baby product up to 9.4%, bath products up to 4.5%, and in skin cleansing products up to 33.2%. PEG-4 dilaurate and PEG-8 dilaurate were reported to be used up to 25% in 1984, and are currently used up to 12% and 15%, respectively. The rest of the ingredients were reported to be used at 15% or less.

Neither PEG-8 dioleate nor PEG-8 dilaurate at 5% enhanced the dermal penetration of ketoprofen through mouse skin when added to a drug delivery plaster preparation. PEG-12 dioleate at 5% did enhance the dermal penetration of ketoprofen with an ER of 1.54±0.22.

The oral LD_{50} of PEG-4 diheptanoate for rats ranged from >2-25 g/kg.

Vaporized PEG-4 diheptanoate was lethal within 4 h to rats at 14.2 mg/L but not at 13.7 mg/L. Clinical signs included salivation, red nasal discharge, and irregular respiration during the exposure period. The rats recovered quickly during the recovery period.

There were no adverse effects observed when 1 g/kg PEG-4 diheptanoate was administered by gavage to rats for 28 consecutive days.

In the repeated inhalation exposure of PEG-4 diheptanoate at 1.0 mg/L) for 6 h/day, 5 days/week for 4 weeks, clinical signs for rats were mild salivation, reduced response to auditory stimulation, and shallow, rapid respiration sporadically during the exposure periods.

PEG-4 diheptanoate was not mutagenic in a reverse mutation assay up to 10 000 µg/plate using *S. typhimurium* or in a mammalian cell gene mutation assay using Chinese hamster ovary cells up to 23.9 mM.

At 100%, PEG-4 diheptanoate caused slight to moderate erythema and edema when administered to rabbit skin for 24 h. There was no skin irritation observed in guinea pigs treated with PEG-4 diheptanoate at 5% or 25% but mild irritation was observed in 1 of 3 guinea pigs at 50% and in 3 of 3 at 100%.

There were no lasting reactions observed when PEG-4 diheptanoate at 100% was administered in the conjunctival sac of rabbits.

In dermal sensitization study using guinea pigs, PEG-4 diheptanoate at 5% or 25% was not sensitizing when challenged at 5% or 50%.

DISCUSSION

Discussion will be developed at the December, 2014 Panel meeting.

CONCLUSION

Conclusion will be developed at the December, 2014 Panel meeting.

TABLES AND FIGURES

Table 1. The definitions and functions of the PEG diesters in this safety assessment.[28]

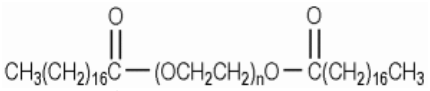
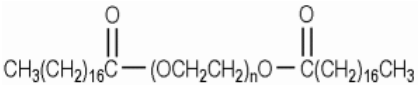
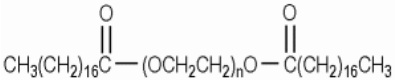
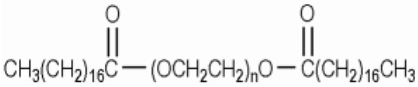
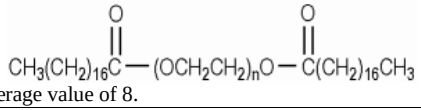
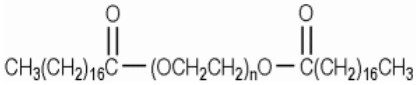
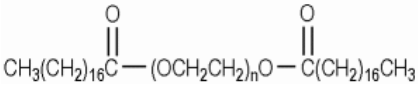
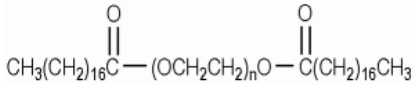
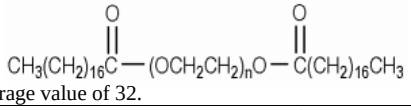
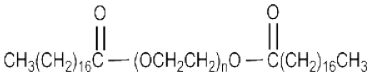
Ingredient and CAS No.	Definition/structure	Function
PEG-2 distearate 109-30-8 52668-97-0 9005-08-7 (generic)	PEG-2 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 2.	Surfactant – emulsifying agent
PEG-3 distearate 9005-08-7 (generic)	PEG-3 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 3.	Surfactant – emulsifying agent
PEG-4 distearate 142-20-1 9005-08-7 (generic)	PEG-4 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 4.	Surfactant – emulsifying agent
PEG-6 distearate 9005-08-7 (generic)	PEG-6 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 6.	Surfactant – emulsifying agent
PEG-8 distearate 9005-08-7 (generic)	PEG-8 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 8.	Surfactant – emulsifying agent
PEG-9 distearate 109-34-2 9005-08-7 (generic)	PEG-9 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 9.	Surfactant – emulsifying agent
PEG-12 distearate 9005-08-7 (generic)	PEG-12 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 12.	Surfactant – emulsifying agent
PEG-20 distearate 9005-08-7 (generic)	PEG-20 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 20.	Surfactant – emulsifying agent
PEG-32 distearate 9005-08-7 (generic)	PEG-32 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 32.	Surfactant – emulsifying agent
PEG-40 distearate 9005-08-7 (generic)	PEG-40 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 40.	Surfactant – emulsifying agent

Table 1. The definitions and functions of the PEG diesters in this safety assessment.[28]

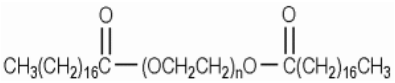
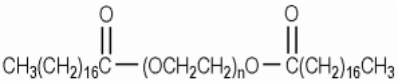
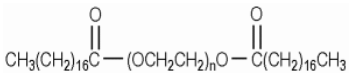
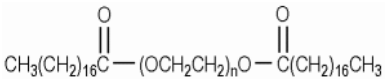
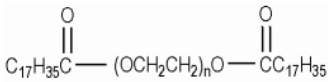
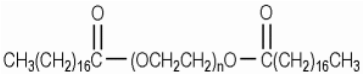
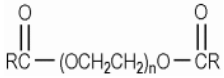
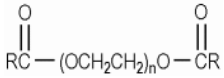
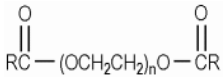
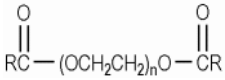
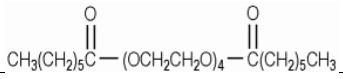
Ingredient and CAS No.	Definition/structure	Function
PEG-75 distearate 9005-08-7 (generic)	PEG-75 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 75.	Surfactant – emulsifying agent; surfactant – solubilizing agent
PEG-120 distearate 9005-08-7 (generic)	PEG-120 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 120.	Surfactant – emulsifying agent; surfactant – solubilizing agent
PEG-150 distearate 9005-08-7 (generic)	PEG-150 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 150.	Surfactant – cleansing agent; surfactant – solubilizing agent
PEG-175 distearate 9005-08-7 (generic)	PEG-175 distearate is the polyethylene glycol diester of stearic acid that conforms to the formula:  where n has an average value of 175.	Surfactant – cleansing agent; surfactant – solubilizing agent
PEG-190 distearate 9005-08-7 (generic)	PEG-190 distearate is the polyethylene glycol diester of stearic acid that conforms generally to the formula:  where n has an average value of 190.	Surfactant – cleansing agent; surfactant – emulsifying agent; surfactant – solubilizing agent; viscosity increasing agent – aqueous
PEG-250 distearate 9005-08-7 (generic)	PEG-250 distearate is the polyethylene glycol diester of stearic acid that conforms generally to the formula:  where n has an average value of 250.	Surfactant – cleansing agent; surfactant – solubilizing agent
PEG-150 dibehenate No CAS No.	PEG-150 dibehenate is the polyethylene glycol diester of behenic acid that conforms generally to the formula:  where n has an average value of 150.	Surfactant – cleansing agent; surfactant – solubilizing agent
PEG-3 dicaprylate/caprate 68583-52-8	PEG-3 dicaprylate/caprate is the polyethylene glycol diester of a mixture of caprylic and capric acids containing an average of 3 moles of ethylene oxide  where n has an average value of 3 and RCO- represents the residue of either caprylic or capric acid.	Surfactant – emulsifying agent
PEG-4 dicocoate 69278-77-9	PEG-4 dicocoate is the polyethylene glycol diester of coconut acid that conforms generally to the formula:  where n has an average value of 4 and RCO- represents the fatty acids derived from coconut oil.	Skin-conditioning agent – emollient; surfactant – emulsifying agent
PEG-8 dicocoate No CAS No.	PEG-8 dicocoate is the polyethylene glycol diester of coconut acid that conforms generally to the formula:  where n has an average value of 8 and RCO- represents the fatty acids derived from coconut oil.	Surfactant – emulsifying agent
PEG-4 diheptanoate 70729-68-9	PEG-4 diheptanoate is the polyethylene glycol diester of heptanoic acid that conforms to the formula: 	Skin-conditioning agent – emollient; surfactant – emulsifying agent

Table 1. The definitions and functions of the PEG diesters in this safety assessment.[28]

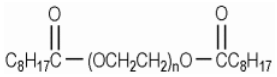
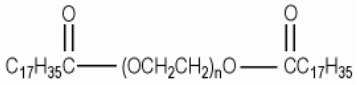
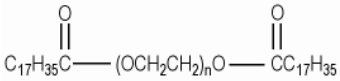
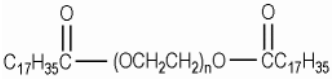
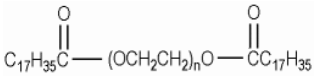
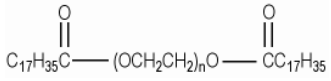
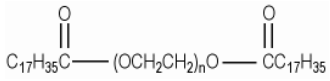
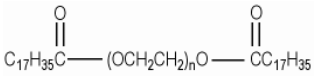
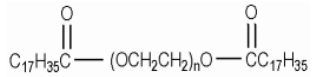
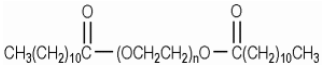
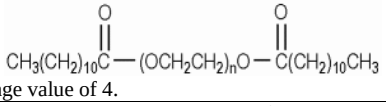
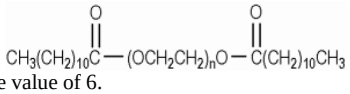
Ingredient and CAS No.	Definition/structure	Function
PEG-2 diisononanoate No CAS No.	PEG-2 diisononanoate is the polyethylene glycol diester of isononanoic acid that conforms to the formula:  where n has an average value of 2.	Surfactant – emulsifying agent
PEG-2 diisostearate No CAS No.	PEG-2 diisostearate is the polyethylene glycol diester of isostearic acid that conforms generally to the formula:  where n has an average value of 2.	Surfactant – emulsifying agent
PEG-3 diisostearate No CAS No.	PEG-3 diisostearate is the polyethylene glycol diester of isostearic acid that conforms generally to the formula:  where n has an average value of 3.	Surfactant – emulsifying agent
PEG-4 diisostearate No CAS No.	PEG-4 diisostearate is the polyethylene glycol diester of isostearic acid that conforms generally to the formula:  where n has an average value of 4.	Surfactant – emulsifying agent
PEG-6 diisostearate No CAS No.	PEG-6 diisostearate is the polyethylene glycol diester of isostearic acid that conforms generally to the formula:  where n has an average value of 6.	Surfactant – emulsifying agent
PEG-8 diisostearate No CAS No.	PEG-8 diisostearate is the polyethylene glycol diester of isostearic acid that conforms to the formula:  where n has an average value of 8.	Surfactant – emulsifying agent
PEG-12 diisostearate No CAS No.	PEG-12 diisostearate is the polyethylene glycol diester of isostearic acid that conforms generally to the formula:  where n has an average value of 12.	Surfactant – emulsifying agent
PEG-90 diisostearate No CAS No.	PEG-90 diisostearate is the polyethylene glycol diester of isostearic acid that conforms generally to the formula:  where n has an average value of 90.	Surfactant – cleansing agent
PEG-175 diisostearate No CAS No.	PEG-175 diisostearate is the polyethylene glycol diester of isostearic acid that conforms generally to the formula:  where n has an average value of 175.	Surfactant – emulsifying agent; viscosity increasing agent – aqueous
PEG-2 dilaurate 6281-04-5 9005-02-1 (generic)	PEG-2 dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 2.	Surfactant – emulsifying agent
PEG-4 dilaurate 9005-02-1 (generic)	PEG-4 dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 4.	Surfactant – emulsifying agent
PEG-6 dilaurate 9005-02-1 (generic)	PEG-6 dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 6.	Surfactant – emulsifying agent

Table 1. The definitions and functions of the PEG diesters in this safety assessment.[28]

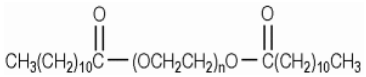
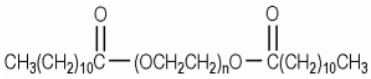
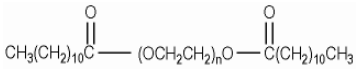
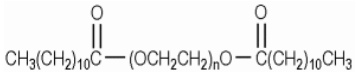
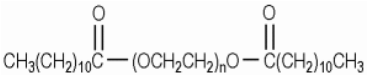
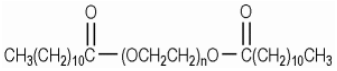
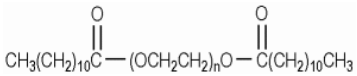
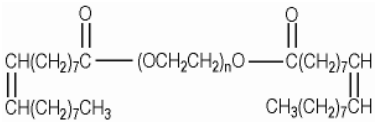
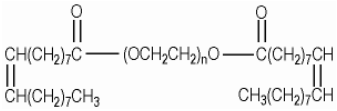
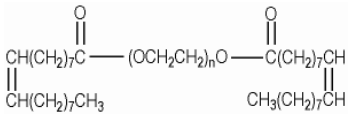
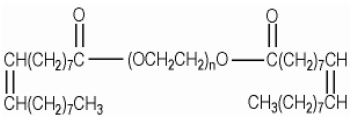
Ingredient and CAS No.	Definition/structure	Function
PEG-8 dilaurate 9005-02-1 (generic)	PEG-8 Dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 8.	Surfactant – emulsifying agent
PEG-12 dilaurate 9005-02-1 (generic)	PEG-12 Dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 12.	Surfactant – emulsifying agent
PEG-16 dilaurate 9005-02-1 (generic)	PEG-16 Dilaurate is the polyethylene glycol diester of lauric acid that conforms generally to the formula:  where n has an average value of 16.	Surfactant – emulsifying agent
PEG-20 dilaurate 9005-02-1 (generic)	PEG-20 dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 20.	Surfactant – emulsifying agent
PEG-32 dilaurate 9005-02-1 (generic)	PEG-32 dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 32.	Surfactant – emulsifying agent
PEG-75 dilaurate 9005-02-1 (generic)	PEG-75 dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 75.	Surfactant – cleansing agent; surfactant – solubilizing agent
PEG-150 dilaurate 9005-02-1 (generic)	PEG-150 dilaurate is the polyethylene glycol diester of lauric acid that conforms to the formula:  where n has an average value of 150.	Surfactant – cleansing agent; surfactant – solubilizing agent
PEG-2 dioleate No CAS No.	PEG-2 dioleate is the polyethylene glycol diester of oleic acid that conforms generally to the formula:  where n has an average value of 2.	Surfactant – emulsifying agent
PEG-3 dioleate No CAS No.	PEG-3 dioleate is the polyethylene glycol diester of oleic acid that conforms generally to the formula:  where n has an average value of 3.	Surfactant – emulsifying agent
PEG-4 dioleate 134141-38-1 52668-97-0 (generic) 9005-07-6 (generic)	PEG-4 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 4.	Surfactant – emulsifying agent
PEG-6 dioleate 52668-97-0 (generic) 9005-07-6 (generic)	PEG-6 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 6.	Surfactant – emulsifying agent

Table 1. The definitions and functions of the PEG diesters in this safety assessment.[28]

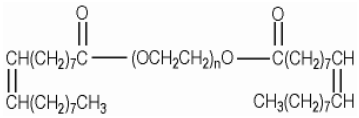
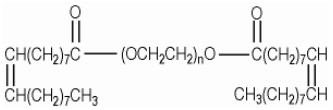
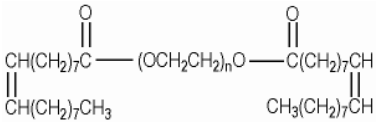
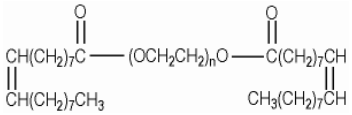
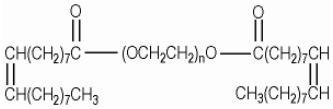
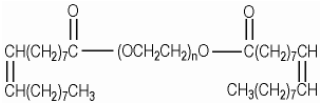
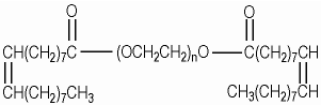
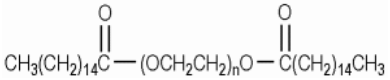
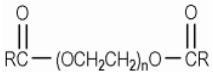
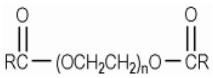
Ingredient and CAS No.	Definition/structure	Function
PEG-8 dioleate 52668-97-0 (generic) 9005-07-6 (generic)	PEG-8 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 8.	Surfactant – emulsifying agent
PEG-10 dioleate 52668-97-0 (generic) 9005-07-6 (generic)	PEG-10 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 10.	Surfactant – emulsifying agent
PEG-12 dioleate 52668-97-0 (generic) 9005-07-6 (generic)	PEG-12 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 12.	Surfactant – emulsifying agent
PEG-20 dioleate 52668-97-0 (generic) 9005-07-6 (generic)	PEG-20 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 20.	Surfactant – emulsifying agent
PEG-32 dioleate 52668-97-0 (generic) 9005-07-6 (generic)	PEG-32 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 32.	Surfactant – emulsifying agent
PEG-75 dioleate 52668-97-0 (generic) 9005-07-6 (generic)	PEG-75 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 75.	Surfactant – cleansing agent; surfactant – solubilizing agent
PEG-150 dioleate 52668-97-0 (generic) 9005-07-6 (generic)	PEG-150 dioleate is the polyethylene glycol diester of oleic acid that conforms to the formula:  where n has an average value of 150.	Surfactant – cleansing agent
PEG-3 dipalmitate 32628-06-1 (generic)	PEG-3 dipalmitate is the polyethylene glycol diester of palmitic acid that conforms generally to the formula:  where n has an average value of 3.	Surfactant – emulsifying agent
PEG-8 ditallate 61791-01-3 (generic)	PEG-8 ditallate is the polyethylene glycol diester of tall oil acid that conforms generally to the formula:  where RCO- represents the tall oil fatty radicals and n has an average value of 8.	Surfactant – emulsifying agent
PEG-12 ditallate 61791-01-3 (generic)	PEG-12 ditallate is the polyethylene glycol diester of tall oil acid that conforms generally to the formula:  where RCO- represents the tall oil fatty radicals and n has an average value of 12.	Surfactant – emulsifying agent

Table 2. Previous safety assessment of PEG diesters and component moieties of the ingredients in this safety assessment.

Ingredients	Conclusion	Maximum concentration	Reference
Previous safety assessment of PEG diesters			
PEG diesters - PEG-2 distearate, PEG-3 distearate, PEG-4 distearate, PEG-6 distearate, PEG-8 distearate, PEG-9 distearate, PEG-12 distearate PEG-20 distearate, PEG-32 distearate, PEG-50 distearate, PEG-75 distearate, PEG-120 distearate, PEG-150 distearate, PEG-175 distearate	Safe for use in cosmetic formulations under the present practices of use.	5%	1
PEG Dilaurates – PEG-2 dilaurate, PEG-4 dilaurate, PEG-6 dilaurate, PEG-8 dilaurate, PEG-12 dilaurate, PEG-16 dilaurate, PEG-20 dilaurate, PEG-32 dilaurate, PEG-75 dilaurate, PEG-150 dilaurate (also included PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE)	Safe for use in cosmetics at concentrations up to 25%.	25%	2
PEG-2 diisononanoate (included with nonanoic and and its nonanoate esters)	Safe as cosmetic ingredients in the present practices of use and concentration described in this safety assessment	74%	3
Safety assessments on related moieties			
Coconut oil, acid and related ingredients	Safe as used	100%	4-6,13
Isostearic acid	Safe as used.	26%	6,8
Oleic acid, lauric acid, stearic acid	Safe as used.	> 50%; 43%	7,9
PEGS	Safe as used.		10-12
PEG stearates	Safe as used.	25%	6,15
Stearates	Safe as used	87%	6,14
Steareths	Safe when formulated to be nonirritating	25%; 32% in products diluted for the bath	17-19
Tall oil acid, sodium tallate, potassium tallate, ammonium tallate	Safe as used.	8%	16

Table 3. Current and historical frequency and concentration of use of PEG diesters according to duration and exposure.[27,29]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2014	**1996**	**2014**	**1995**	**2014**	**1996**	**2014**	**1995**
	PEG-2 distearate				**PEG-3 distearate**			
Totals*	**6**	**4**	**0.001**	**NR**	**50**	**8**	**0.45-3.4**	**NR**
Duration of Use								
Leave-On	*6*	*4*	*0.001*	*NR*	*NR*	*2*	*0.45-1.5*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*50*	*6*	*0.45-3.4*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*1.7*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2[a]; 2[c]	2[a]; 2[c]	NR	NR	NR	2[c]	NR	NR
Incidental Inhalation-Powder	2[c]	2[c]	NR	NR	NR	2[c]	NR	NR
Dermal Contact	6	4	0.001	NR	35	6	0.45-3	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	15	2	1-3.4	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	2.8	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	0.45-1.7	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	2014	**1996**	**2014**	**1995**	**2014**	**1996**	**2014**	**1995**
	PEG-4 distearate				**PEG-6 distearate**			
Totals*	**1**	**5**	**NR**	**NR**	**1**	**1**	**0.5-1**	**NR**
Duration of Use								
Leave-On	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*0.5-1*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*1*	*1*	*0.91-1*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	1[b]	NR
Dermal Contact	NR	1	NR	NR	1	1	0.5-1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	4	NR	NR	NR	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	2014	**1996**	**2014**	**1995**	**2014**	**1996**	**2014**	**1995**
	PEG-8 distearate				**PEG-12 distearate**			
Totals*	**48**	**64**	**0.0091-7**	**NR**	**7**	**13**	**0.2-1.7**	**NR**
Duration of Use								
Leave-On	*37*	*23*	*0.0091-6.5*	*NR*	*1*	*2*	*NR*	*NR*
Rinse-Off	*11*	*41*	*7*	*NR*	*6*	*11*	*0.2-1.7*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	2	NR	0.0091-1.2	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	5[a]; 3[c]	2[a]; 3[c]	0.3[a]	NR	1[a]	NR	NR	NR
Incidental Inhalation-Powder	3[c]	1; 3[c]	0.5[b]	NR	NR	NR	NR	NR
Dermal Contact	43	50	0.0091-7	NR	1	1	NR	NR
Deodorant (underarm)	10[a]	6[a]	1-6.5[d]	NR	NR	NR	NR	NR
Hair - Non-Coloring	5	NR	NR	NR	6	12	0.2-1.7	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	4	26	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 3. Current and historical frequency and concentration of use of PEG diesters according to duration and exposure.[27,29]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2014	**1996**	**2014**	**1995**	**2014**	**1996**	**2014**	**1995**
	PEG-120 distearate				**PEG-150 distearate**			
Totals*	**7**	**NR**	**NR**	**NR**	**654**	**187**	**0.003-33.2**	**1-5**
Duration of Use								
Leave-On	*NR*	*NR*	*NR*	*NR*	*51*	*59*	*0.024-9.4*	*1-5*
Rinse-Off	*7*	*NR*	*NR*	*NR*	*569*	*101*	*0.0003-33.2*	*1-5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*34*	*27*	*1-1.5*	*1.75*
Exposure Type								
Eye Area	NR	NR	NR	NR	6	2	0.07-1.8	0.5
Incidental Ingestion	NR	NR	NR	NR	NR	NR	0.05	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	13[a]; 12[c]	10[a]; 2[c]	0.006-2.4[a]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	1; 12[c]	4; 2[c]	0.024-9[b]	NR
Dermal Contact	7	NR	NR	NR	464	117	0.0003-33.2	1-5
Deodorant (underarm)	NR	NR	NR	NR	1[a]	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	189	69	0.06-4	1-5
Hair-Coloring	NR	NR	NR	NR	NR	NR	0.0075-0.15	NR
Nail	NR	NR	NR	NR	NR	1	NR	NR
Mucous Membrane	NR	NR	NR	NR	375	42	0.0003-4.5	1.75
Baby Products	NR	NR	NR	NR	25	14	0.75-9.4	NR

	2014	**1996**	**2014**	**1995**	**2014**	**2009**	**2014**	**2009**
	PEG-175 distearate				**PEG-2 diisononanoate**			
Totals*	**NR**	**NR**	**0.089**	**NR**	**NR**	**NR**	**1.7**	**2**
Duration of Use								
Leave-On	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*1.7*	*2*
Rinse-Off	*NR*	*NR*	*0.089*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	0.089	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	1.7	2
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 3. Current and historical frequency and concentration of use of PEG diesters according to duration and exposure.[27,29]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2014	**1996**	**2014**	**1984**	**2014**	**1996**	**2014**	**1984**
	PEG-4 dilaurate				**PEG-8 dilaurate**			
Totals*	**NR**	**15**	**0.028-12**	**1-25[f]**	**14**	**25**	**0.05-15**	**0.1-25[f]**
Duration of Use								
Leave-On	*NR*	*5*	*0.032-12*	*NR*	*5*	*9*	*6*	*NR*
Rinse-Off	*NR*	*1*	*0.028-0.72*	*NR*	*3*	*9*	*0.18-6*	*NR*
Diluted for (Bath) Use	*NR*	*9*	*NR*	*NR*	*6*	*7*	*0.05-15*	*NR*
Exposure Type								
Eye Area	NR	NR	0.04-2	NR	2	NR	0.18	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	2[a]; 1[c]	0.072[e]; 0.36[a]	NR	5[a]	NR	6[a]	NR
Incidental Inhalation-Powder	NR	1[c]	0.25-0.36[b]	NR	NR	NR	NR	NR
Dermal Contact	NR	15	0.028-12	NR	9	11	0.05-15	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	0.036-0.72	NR	5	13	6	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	1	NR	NR
Mucous Membrane	NR	9	NR	NR	6	7	0.05-15	NR
Baby Products	NR	NR	NR	NR	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.

NR – no reported use [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] Not spray

[e] Pump spray

[f] Details of the concentration of use data were not included in the original report.

Table 4. Frequency of use according to duration and exposure of *A. millefolium*-derived ingredients.[27,29]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	PEG-250 distearate		**PEG-8 dicocoate**		**PEG-4 diheptanoate**		**PEG-6 diisostearate**	
Total/range	**21**	**NR**	**NR**	**0.04-0.08**	**19**	**0.02-14.3**	**1**	**NR**
Duration of use								
Leave-on	NR	NR	NR	0.04	19	0.02-14.03		NR
Rinse-off	16	NR	NR	0.04-0.08	NR	NR	1	NR
Diluted for (bath) use	5	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	5	0.4-8	NR	NR
Incidental ingestion	NR	NR	NR	NR	9	0.07-14	NR	NR
Incidental Inhalation-sprays	NR	NR	NR	0.04[a]	2[a]; 2[c]	NR	NR	NR
Incidental inhalation-powders	NR	NR	NR	NR	2[c]	14.3[b]	NR	NR
Dermal contact	21	NR	NR	0.04-0.08	10	0.02-14.3	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	0.04	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	21	NR	NR	NR	9	0.07-14	1	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

	PEG-8 diisostearate		**PEG-12 diisostearate**		**PEG-90 diisostearate**		**PEG-175 diisostearate**	
Total/range	**12**	**0.5-4.5**	**5**	**2.3-10**	**11**	**0.029-2.1**	**1**	**5**
Duration of use								
Leave-on	4	0.5-2	NR	4	2	2.1	1	NR
Rinse-off	8	1.5-4.5	5	2.3-10	8	0.029	NR	5
Diluted for (bath) use	NR	NR	NR	NR	1	NR	NR	NR
Exposure type								
Eye area	2	4.5	1	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	3[c]	NR	NR	4[a]	NR	NR	NR	NR
Incidental inhalation-powders	3[c]	0.5[b]	NR	NR	NR	NR	NR	NR
Dermal contact	12	0.5-4.5	5	2.3-10	11	0.029	1	5
Deodorant (underarm)	NR	2[d]	NR	NR	2[a]	2.1[e]	NR	NR
Hair-noncoloring	NR	NR	NR	4	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	9	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

Table 4. Frequency of use according to duration and exposure of *A. millefolium*-derived ingredients.[27,29]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	PEG-8 dioleate		PEG-12 dioleate					
Total/range	**4**	**1-5**	**2**	**0.024-4.5**				
Duration of use								
Leave-on	2	1	NR	0.024-4.5				
Rinse-off	2	5	1	0.12-1				
Diluted for (bath) use	NR	NR	1	NR				
Exposure type								
Eye area	2	1	NR	NR				
Incidental ingestion	NR	NR	NR	NR				
Incidental Inhalation-sprays	NR	NR	NR	0.024[e]; 0.024[a]				
Incidental inhalation-powders	NR	NR	NR	0.14-0.15[b]				
Dermal contact	2	5	2	0.1-4.5				
Deodorant (underarm)	NR	NR	NR	NR				
Hair-noncoloring	NR	NR	NR	0.024-0.12				
Hair-coloring	NR	NR	NR	NR				
Nail	NR	NR	NR	NR				
Mucous Membrane	2	NR	1	NR				
Baby	NR	NR	NR	NR				

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum 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] Not spray

[e] Pump hair spray

Table 5. Ingredient not reported to be in current use.[27,29]

PEG-9 distearate	PEG-20 distearate	PEG-32 distearate
PEG-75 distearate	PEG-40 distearate	PEG-190 distearate
PEG-150 dibehenate	PEG-3 dicaprylate/caprate	PEG-4 dicocoate
PEG-2 diisostearate	PEG-3 diisostearate	PEG-4 diisostearate
PEG-2 dilaurate	PEG-6 dilaurate	PEG-12 dilaurate
PEG-16 dilaurate	PEG-20 dilaurate	PEG-32 dilaurate
PEG-75 dilaurate	PEG-150 dilaurate	PEG-2 dioleate
PEG-3 dioleate	PEG-4 dioleate	PEG-6 dioleate
PEG-10 dioleate	PEG-20 dioleate	PEG-32 dioleate
PEG-75 dioleate	PEG-150 dioleate	PEG-3 dipalmitate
PEG-8 ditallate	PEG-12 ditallate	

Table 6. FDA Code of Federal Regulations that apply to the PEG diesters in this safety assessment.

Use related to food	Ingredients	Code
Can be used for coloring shell eggs if there is no penetration of the shell.	PEG-2 distearate	21CFR73.1
May be used as defoaming agents in food as an emulsifier not to exceed 10% by weight of defoamer formulation.	PEG-8 dioleate; PEG-12 dioleate	21CFR173.340
May be used as indirect food additives: adhesives.	PEG-4 distearate; PEG-6 distearate; PEG-8 distearate; PEG-9 distearate; PEG-12 distearate; PEG-20 distearate; PEG-8 dicocoate; PEG-4 dilaurate; PEG-6 dilaurate; PEG-8 dilaurate; PEG-12 dilaurate; PEG-4 dioleate PEG-6 dioleate; PEG-8 dioleate; PEG-10 dioleate; PEG-12 dioleate; PEG-8 ditallate; PEG-12 ditallate	21CFR175.105
May be used as paper and paperboard components of paper and paperboard in contact with aqueous and fatty foods.	PEG-8 dioleate; PEG-4 dilaurate	21CFR176.170
May be used as paper and paperboard substances for use only as components of paper and paperboard; components of paper and paperboard in contact with dry food.	PEG-4 dilaurate	21CFR176.180
May be used as paper and paperboard substances for use only as components of paper and paperboard; defoaming agents used in coatings.	PEG-8 dioleate; PEG-4 dilaurate; PEG-12 dioleate	21CFR176.200
May be used as paper and paperboard substances for use only as components of paper and paperboard; defoaming agents used in the manufacture of paper and paperboard.	PEG-4 distearate; PEG-6 distearate; PEG-8 distearate; PEG-12 distearate; PEG-20 distearate; PEG-32 distearate; PEG-8 dicocoate; PEG-2 dilaurate; PEG-4 dilaurate; PEG-6 dilaurate; PEG-8 dilaurate; PEG-12 dilaurate; PEG-20 dilaurate; PEG-4 dioleate; PEG-6dioleate; PEG-8 dioleate; PEG-12 dioleate; PEG-20 dioleate; PEG-32 dioleate; PEG-8 ditallate; PEG-12 ditallate	21CFR176.210
May be used as indirect food additives: polymers. Substances for use as basic components of single and repeated use food contact surfaces; closures with sealing gaskets for food containers.	PEG-8 distearate; PEG-8 dioleate; PEG-8 dicocoate; PEG-8 dilaurate; PEG-8 ditallate	21CFR177.1210
May be used as indirect food additives: polymers. Substances for use as basic components of single and repeated use food contact surfaces; filters, resin-bonded.	PEG-8 distearate; PEG-9 distearate; PEG-12 distearate; PEG-20 distearate; PEG-32 distearate; PEG-8 dicocoate; PEG-8 dilaurate; PEG-12 dilaurate; PEG-20 dilaurate; PEG-32 dilaurate; PEG-8 dioleate; PEG-10 dioleate; PEG-12 dioleate; PEG-20 dioleate; PEG-32 dioleate	21CFR177.2260
May be used as indirect food additives: polymers. Substances for use as basic components of single and repeated use; rubber articles intended for repeated use.	PEG-3 dicaprylate/caprate	21CFR177.2600
May be used as indirect food additives: polymers. Substances for use as basic components of single and repeated use; textiles and textile fibers.	PEG-8 distearate; PEG-9 distearate; PEG-12 distearate; PEG-20 distearate; PEG-32 distearate; PEG-8 dicocoate; PEG-2 dilaurate; PEG-8 dilaurate; PEG-12 dilaurate; PEG-20 dilaurate; PEG-32 dilaurate; PEG-8 dioleate; PEG-12 dioleate; PEG-20 dioleate; PEG-32 dioleate; PEG-8 ditallate; PEG-12 ditallate	21CFR177.2800
Food additives permitted in feed and drinking water of animals.	PEG-8 dioleate	21CFR573.800
Food additives permitted in feed and drinking water of animals: The food additive polyoxyethylene glycol (400) mono- and dioleates may be safely used as an emulsifier in calf-milk replacer formulations.	PEG-8 dioleate	21CFR573.820

Table 7. Acute toxicity studies of PEG-4 diheptanoate.

Animal (n)	Results	Comments	Reference
Crl:CD rats (10/sex)	Oral LD_{50} was 25 g/kg for female rats and >25 g/kg for male rats	Clinical signs included labored breathing, belly-to-cage posture, lacrimation, staining of the face, stained and wet perineal area, and weight loss. All deaths occurred within 2 days of dosing.	[21]
Wistar rats (5/sex)	Oral LD_{50} >2 g/kg	There was no mortality reported. Weight gains were normal in all rats. Gross pathological examination at necropsy revealed no treatment-related findings. There were no abnormal clinical signs observed except slight piloerection and sporadic findings (e.g., ventral or limb position, reduced activity, reduced turgor) up to 6 hrs after oral administration.	[35]
Male Chr:CD rats (10)	Oral LD_{50} >25 g/kg	One mortality occurred on the day after dosing. Clinical signs included only hyperemia, lethargy, and prostration. No systemic toxicity or adverse effects were reported. No gross abnormalities or lesions were observed. Slight initial weight loss was observed. No necropsies were performed.	[35]
Female Crl:CD rats (10)	Oral LD_{50} estimated to be 24-25 g/kg	Test doses: 14, 19, 22, 23, 24, 24.5, 24.75, 24.9 and 25 g/kg in corn oil. Mortalities at each dose level: 0/10, 0/10, 0/10, 0/10, 4/10, 1/10, 2/10, and 10/10, respectively. All deaths occurred within 2 days. Clinical signs, observed at all dose levels, included flat body posture, moribund condition, labored breathing, stained/wet perineal area, lacrimation, stained face, weakness, ataxia, lethargy, prostration, salivation and chromodacryorrhea. Body weight decrease was observed at all dose levels. No necropsies were performed.	[35]

Table 8. Genotoxicity assays of PEG-4 diheptanoate.[35]

Assay	Concentration	Results
Bacterial reverse mutation assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537	500-10 000 µg/plate, 100-2500 µg/plate (based on toxicity with TA1535). OECD 471 with independent repeat. Positive Control: N-methyl-N'-nitro-N-nitroguanidine (TA100 and TA1535 without S9), 9-aminoacridine (TA1537 without S9), 2-nitrofluorene (TA98 without S9) and 2-aminoanthracene (all strains with S9).	Negative with and without metabolic activation
Mammalian cell gene mutation assay using Chinese hamster ovary cells	-S9: 0.27-23.9 mM, +S9: 0.25-23.9 mM. 3 independent tests; duplicate cultures/treatment.	Negative with and without metabolic activation

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Final Report on the Safety Assessment of PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate'

PEG Distearate compounds are the polyethylene glycol (PEG) diesters of Stearic Acid. They are manufactured by the esterification of Stearic Acid with a the number of moles of ethylene oxide corresponding to the average polyethylene glycol chain length desired. PEGs Distearate are used as emulsifying, cleansing, and solubilizing agents in a wide variety of cosmetic formulations. Not all of the polymer chain lengths covered in this assessment are currently reported to be used, but all are listed as cosmetic ingredients and may have been used in the past and could be used in the future. Very little toxicity data are available for the PEGs Distearate. Related compounds including PEGs, PEGs Stearate, Steareths, and Stearic Acid, have previously been reviewed. In general, PEGs have a low level of toxicity whether the exposure is oral or dermal. Minimal ocular irritation is seen with PEGs, PEGs Stearate, Steareths, and Stearic Acid. No evidence of mutagenicity, carcinogenicity, or reproductive and developmental toxicity of these related compounds was found. Based on clinical data in bum patients, PEGs were mild irritant/sensitizers and there was evidence of nephrotoxicity. Cosmetic manufacturers should continue to adjust product formulations to minimize any untoward effects when products are used on damaged skin. PEGs Stearate, Steareths, and Stearic Acid were not irritants, sensitizers, or phototoxins. Because of the possibility of residual ethylene oxide and/or 1,4-dioxane impurities in PEGs Distearate, cosmetic formulators are urged to continue efforts to remove these impurities before blending PEGs Distearate into cosmetic formulations. Although metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins, it was considered unlikely that the relevant metabolites would be found in or produced from the use of PEGs Distearate in cosmetic formulations. Based on the available data on related compounds, and current industry practices in the use and manufacture of PEGs Distearate, it was concluded that PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are safe for use in cosmetic formulations under the present practices of use.

INTRODUCTION

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are surfactants used in cosmetics as emulsifying, cleansing, and solubilizing agents. Chemically, these ingredients are the polyethylene glycol (PEG) diesters of Stearic Acid. Note that the different chain length PEGs are formed by condensing ethylene oxide and water, with the average number of moles of ethylene oxide used corresponding to the number in the name.

Related chemicals (PEG, Stearic Acid, the Steareths, and PEG Stearates) have been reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel and Final Reports have been published. The following conclusions were made:

> PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates are safe as cosmetic ingredients in the present practices of concentration and use (Elder 1983).
>
> PEG -6, -8, -32, -75, 150, -14M, and -20M are safe for use at the concentrations reflected in the Cosmetic Use section and in the product formulation safety test data included in the Final Report. The Expert Panel recommends that cosmetic formulations containing these PEGs not be used on damaged skin (Andersen 1993).
>
> Stearic Acid is safe for use as a cosmetic ingredient (Elder 1987).
>
> Steareth-2, -4, -6, -7, -10, -1 I, -13, -15, and -20 are safe as cosmetic ingredients in the present practices of use and concentration (Elder 1988).

The relevant data from these previous Final Reports have been summarized in this review as a further basis for the assessment of safety of PEG-2- 175 Distearate.

CHEMISTRY

Definition and Structure

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 (CAS No. 9005-08-7 [generic]) Distearate are the polyethylene glycol diesters of Stearic Acid. These ingredients conform to the formula shown in Figure 1, where n has the average value of the number in the name (Wenninger and McEwen 1997).

Chemical and Physical Properties

The PEG Distearate group of cosmetic ingredients has a broad range of properties depending on the degree of polymerization of the PEG segment. The physical forms of these ingredients range from liquids to solids or flakes. Solubility properties are also dependent on the length of the PEG component. Typically, these ingredients are soluble in oil and hydrocarbon solvents when less than eight ethylene oxide units are present. Solubility in water begins with compounds containing 12-15 ethylene oxide units. Specific gravity and viscosity increase with increasing ethylene oxide content (Budavari 1989).

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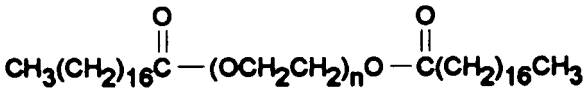

FIGURE 1
Chemical formula for the PEGs Distearate polymer (Wenninger and McEwen 1997). n is the average number corresponding to the number in the name.

Method of Manufacture

In general, the PEGs Distearate are manufactured by the esterification of Stearic Acid with ethylene oxide or with polyethylene glycol (Budavari 1989).

Impurities

Production lots of PEG-150 Distearate from different manufacturers had peroxide concentrations of 1.97 and 1.92 μEq thiosulfate/g glycol (McGinity, Hill, and La Via 1975).

Silverstein et al. (1984) reported that PEG-6 may contain small amounts of monomer and dimers. The amounts were not quantified. Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75 (Hamburger, Azaz, and Donbrow 1975). The amount of peroxide in PEGs is dependent upon the molecular weight of the PEG and its age. The older the compound, the greater the concentration of peroxides. In a colorimetric assay used to determine the peroxide concentrations in several production lots of PEGs, PEG-6 and PEG-8 were each added to acidified potassium iodide solution, and the iodine liberated was titrated against a standard thiosulfate solution. PEG-6 had peroxide concentrations ranging from 1.4 to 9.3 μEq thiosulfate/ml glycol. PEG-8 had concentrations ranging from 3.24 to 5.7 μEq thiosulfate/ml glycol. The specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide (McGinity, Hill, and La Via 1975).

Ethoxylated surfactants may also contain 1,4-dioxane, a byproduct of ethoxylation (Robinson and Ciurczak 1980). 1,4-Dioxane is a known animal carcinogen (Kociba et al. 1974; Hoch-Ligeti, Argus, and Arcos 1970; Argus, Arcos, and Hoch-Ligeti 1965). In the CIR safety assessment of the PEG Stearates, the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations. Traces of the reactants, Stearic Acid, ethylene oxide, and the catalytic agents used, may remain in the finished product (Elder 1983).

Reactivity

PEGs Stearate are relatively stable compounds; however, the ether oxygens are potentially reactive and the ester bonds are potentially vulnerable to enzymatic cleavage (Elder 1983).

USE

Cosmetic

The PEGs Distearate are surfactants used as emulsifying, cleansing, and solubilizing agents (Wenninger and McEwen 1997). The product formulation data submitted to the Food and Drug Administration (FDA) in 1996 indicated that PEG-2. -3, -4, -6, -8, -12, -50, and -150 Distearate were in use, and that they were collectively used in 283 cosmetic formulations (Table I) (FDA 1996). Concentration of use data were submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) in 1995; 0.5% to >1–5% PEGs Distearate were used in cosmetic formulations (Table 2) (CTFA 1995).

International

The PEGs Distearate, with the exception of PEG-120 Distearate, are listed in the *Comprehensive Licensing Standards of Cosmetics by Category* (CLS) and must conform to the standards of the *Japanese Cosmetic Ingredient Codex* (JCIC) (Yakuji Nippo, Ltd. 1994).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, Distribution, and Excretion

PEG-40 Stearate is hydrolyzed in vitro by pancreatic lipase. When the same compound was hydrolyzed with alkali, a 5–1000 mg percent concentration range of the polyoxyethylene hydrolysate had no hemolytic effect on defibrinated human blood tested at 37°C for 18 hours. PEG-40 Stearate also produced no significant interference with oxygen uptake by kidney tissue preparations. PEG-20, -30, and -40 Stearate activated the cytochrome oxidase enzyme system in heart muscle preparations up to a concentration of 150 mg/ml (Elder 1983).

Gastrointestinal absorption of PEGs is dependent on the molecular weight of the compound. In general, the larger the molecular weight of the PEG compound, the lesser the absorption that occurs. In both oral and intravenous (i.v.) studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and feces. In a study with human bum patients, monomeric ethylene glycol was isolated in the serum following topical exposure to a PEG-based antimicrobial cream, indicating that PEGs are readily absorbed through damaged skin (Andersen 1993).

In general, fatty acids such as Stearic Acid are absorbed, digested, and transported in animals and humans. Radioactivity from labeled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph. B-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl-CoA. Placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied. High intake of dietary saturated fatty acids has been associated with increased incidence of atherosclerosis and thrombosis (Elder 1987).

ANIMAL TOXICOLOGY

Acute Toxicity

Hopper, Hulpieu, and Cole (1949) reported the toxicological properties of several surface-active agents, including PEG-8 and PEG-20 Distearate. The LD50s for those two compounds were

TABLE 1
Product formulation data (FDA 1996)

Product category	Total no. formulations in category	Total no. formulations containing ingredient
PEG-2 Distearate		
Face and neck preparations (excluding shaving)	300	2
Moisturizing preparations	942	1
Night preparations	226	1
1996 total		**4**
PEG-3 Distearate		
Shampoos (noncoloring)	972	2
Cleansing preparations	820	4
Body and hand preparations (excluding shaving)	1012	2
1996 total		**8**
PEG-4 Distearate		
Hair conditioners (noncoloring)	715	4
Cleansing preparations	820	1
1996 total		**5**
PEG-6 Distearate		
Cleansing preparations	820	1
1996 total		**1**
PEG-8 Distearate		
Hair conditioners	715	9
Rinses (noncoloring)	60	2
Shampoos (noncoloring)	972	1
Tonics, dressings, and other hair grooming aids	60	1
Other hair preparations	395	1
Blushers (all types)	277	1
Face powders	313	1
Other makeup preparations	157	1
Deodorants (underarm)	303	6
Other personal cleanliness products	339	26
Aftershave lotion	268	6
Other shaving preparation products	63	3
Body and hand preparations (excluding shaving)	1012	3
Moisturizing preparations	942	1
Other skin care preparations	810	2
1996 total		**64**
PEG-12 Distearate		
Hair conditioners	715	6
Rinses (noncoloring)	60	5
Tonics, dressings, and other hair grooming aids	604	1
Makeup bases	154	1
1996 total		**13**
PEG-50 Distearate		
Cleansing preparations	820	1
1996 total		**1**

(Continued on next page)

TABLE 1
Product formulation data (FDA 1996) *(Continued)*

Product category	Total no. formulations in category	Total no. formulations containing ingredient
PEG-150 Distearate		
Baby shampoos	23	12
Other baby products	37	2
Bubble baths	211	15
Other bath preparations	166	12
Eye shadow	588	1
Eye lotion	22	1
Hair conditioners (non-coloring)	715	4
Hair straighteners	50	1
Permanent waves	434	1
Shampoos (non-coloring)	972	46
Tonics, dressings, and other hair grooming aids	604	2
Other hair preparations	395	3
Blushers (all types)	277	26
Face powders	313	2
Foundations	355	3
Makeup bases	154	1
Rouges	30	1
Nail creams and lotions	18	1
Bath soaps and detergents	372	14
Other personal cleanliness products	339	1
Aftershave lotion	268	1
Men's talcum	11	2
Shaving cream	158	7
Other shaving preparation products	63	3
Cleansing preparations	820	9
Body and hand preparations (excluding shaving)	1012	2
Moisturizing preparations	942	5
Night preparations	226	1
Paste masks (mud packs)	300	3
Other skin care preparations	810	3
Suntan gels, creams, and liquids	196	1
Indoor tanning preparations	67	1
1996 total		**187**

365 mg/kg and 220 mg/kg, respectively, when determined using rats.

The LD50s were > 10 g/kg for PEG-2 Stearate, > 10 g/kg (in corn oil) and >31.6 g/kg (aqueous) for PEG-8 Stearate, >10 g/kg for PEG-12 Stearate, >10 g/kg and 19.9 g/kg for PEG-20 Stearate. The acute oral LD50 of a hair cream preparation containing 1.5% PEG-6 Stearate was > 34.6 g/kg in rats. The acute intraperitoneal (i.p.) LD50 of PEG-8 Stearate was >9 ml/kg in rats given 2 ml Stearate, > 10 g/kg for PEG-32 Stearate, 32 g/kg for PEG-40 Stearate (vehicle not specified), >25 g/kg for aqueous solutions of both PEG-50 and -100 Stearate, and > 10 g/kg for PEG-150 injections. No signs of toxicity were observed in rats given i.p. injections of 2.5 g/kg PEG-50 Stearate or PEG-100 Stearate. A concentration of 5% PEG-40 Stearate given as a 5-ml injection into the lumen of the jejunem of a dog had no effect on blood pressure. That same day, an i.v. injection produced a prolonged hypotensive response. It was stated that this response was a "characteristic reaction" of the dog to a variety of polyoxyethylene compounds. The acute dermal LD50 of 15% PEG-8 Stearate was > 10 ml/kg in rabbits; the only effect noted was moderate erythema at the application sites at 24 hours which cleared by day 3 (Elder 1983).

Acute oral LD50s for PEGs in rabbits were 17.3 g/kg (100% PEG-6) and 76 g/kg (100% PEG-75). In acute dermal studies, no

TABLE 2
Concentration of use (CTFA 1995)

Formulation	Concentration (%)
Unspecified PEG Distearate	
Hair conditioner	4
Antiperspirant	1
Cleanser	2
Penns	2
Shampoo	1.5
Nail cuticle cream	4
Moisturizer	1.5
PEG-150 Distearate	
Bubble bath, shower gel, liquid soap	up to 1.75
Moisturizing facial lotion, eye cream, moisturizing facial cream, moisturizing night cream	up to 0.5
Hair conditioner	1-5
Hair preparations	>1-5
Skin care preparations	>1-5

deaths were reported in groups of rabbits dosed with 20 ml/kg of either undiluted PEG-6 or 40% PEG-20M (Andersen 1993).

Acute oral toxicity was slight in animals of studies with Stearic Acid at concentrations as great as 10 g/kg, or with cosmetic formulations containing Stearic Acid at concentrations of 2.8-13% at a dose of 15-19 g/kg body weight. Intradermal injections of 10-100 mM Stearic Acid in olive oil produced mild erythema and slight induration of the skin of guinea pigs and rabbits (Elder 1987).

Two of 10 Wistar-derived albino rats died after being given a roll-on antiperspirant orally (containing 1.8% Steareth-2); upon necropsy, one had "fibrous tissue encasing the heart and lungs." The reported LD50 was > 10 g/kg. The acute oral LD50s in rats of Steareth-2 (40% in water), -10 (unspecified concentration), and -20 (25% in distilled water) were >25.1 g/kg, 2.91 g/kg, and 2.07 g/kg, respectively. The acute i.p. LD50 of 10% Steareth-2 in normal saline was 0.76 g/kg in rats; the i.p. LD50 of 1.5% Steareth-20 in a moisturizing formulation was 0.19 g/kg. The acute i.v. LD50 of 1% Steareth-2 in propylene glycol was 0.041 g/kg; that of 10% Steareth-20 in isotonic NaCl was 0.164 g/kg. A single oral dose of 25.1 g/kg Steareth-2 (40% in water) was given to groups of five male and five female Sprague-Dawley rats. The rats had been fasted for 16 hours prior to administration of the test chemical and the subsequent 14-day observation period. None of the rats died during the study (Elder 1988).

Short-Term Toxicity

Weanling hamsters fed a diet containing 5% or 15% PEG Monostearate for 2-10 weeks had pronounced changes in the duodenum, ileum, liver, kidneys, and testes. Severe erosion of the ileal mucosa and necrosis of the liver were observed. Spermatogenic activity was decreased and tubular degeneration occurred in the kidneys. No signs of toxicity were observed in rats, monkeys, mice, and dogs fed diets containing up to 4% PEG-8, -40, -50, or -100 Stearate for periods ranging from 6 to 9 weeks. Rabbits exposed topically for 20 days to 0.5-2.0 g/kg of 1.5% PEG-6 Stearate in a product formulation had erythema, dryness, wrinkling, desquamation, and hyperkeratosis at the application sites. No other signs of toxicity were noted (Elder 1983).

No toxicity was reported in rabbits that received daily topical applications of PEG-20M (0.8 g/kg/day) for 30 days. The only effect noted in the study was transient, mild erythema. The only evidence of systemic toxicity that resulted from dermal exposure was renal failure in rabbits that received repeated applications of an antimicrobial cream containing 63% PEG-6, 5% PEG-20, and 32% PEG-75 to excised skin sites for 7 days (Andersen 1993).

Feeding of 50% Stearic Acid to chicks for 4 weeks had no adverse effects. Rats fed high-fat diets containing 5% Stearic Acid had decreased clotting time, moderate hyperlipemia, and severe phlebothrombosis following initiation with an i.v. injection of lipopolysaccharide (LPS) from *Salmonella typhosa*. In a similar study, rats fed high-fat diets containing 6% Stearic Acid for 9 weeks developed severe aortic atherosclerosis and thrombosis following *S. ryphosa* LPS induction; high mortality was also observed. A diet containing 50% Stearic Acid fed to rats for 8 weeks resulted in a microscopic "foreign body-type reaction" in adipose tissue. Etythema, desquamation, and follicular keratosis were not observed in albino rabbits that received 3 ml daily topical applications (to the skin of the external ear canal) of 5% (*w/v*) Stearic Acid in alcohol 5 days per week for 6 weeks. Doses of 2 ml/kg 20% Stearic Acid in a product formulation applied to abraded and intact skin sites on the back daily for 4 weeks resulted in slight edema and desquamation, but no deaths, in rabbits. Daily topical applications of Stearic Acid (concentration not given) to the shaved skin of albino or Long-Evans rats had little effect after 2 weeks of treatment. Edema, slight desquamation, and slight scaling were observed in New Zealand white rabbits that received topical applications to the skin of the back of a product formulation containing 2% Stearic Acid daily for 4 weeks. Intact and abraded skin sites had similar reactions to the test product. All other physiological parameters were normal and no significant gross or microscopic alterations were observed (Elder 1987).

Subchronic Toxicity

Six large calculi (4-6 mm in diameter; 50-95 mg in weight) were found in the urinary bladders of hamsters fed unspecified PEGs Stearate for 74-260 days. Rabbits fed a diet containing 4% PEG-8 Stearate for 4 months or 5% PEG-8 Stearate for 19 weeks had no treatment-related effects (Elder 1983).

In subchronic, 90-day toxicity studies involving groups of albino rats, the largest (PEG-20M) and smallest (PEG-6) molecular weight PEGs tested did not induce toxicity or death when administered daily in the diet or drinking water, respectively, at concentrations of 4% or less. No evidence of toxicity was observed in rabbits that received topical applications of 2 ml/kg/day of PEG-6 daily, 5 days/week, for 18 weeks (Andersen 1993).

A "foreign body-type reaction" in perigonadal fat and the reversible formation of lipogranulomas were observed in rats fed 50 g/kg/day Stearic Acid for 24 weeks. Stearic Acid at a concentration of 2% in two cosmetic product formulations did not cause dermal irritation in New Zealand white rabbits that received daily 2 ml/kg topical applications, 5 days per week, for 20 weeks to both abraded and intact skin sites on the back. Edema was observed in all test rabbits (6/6) and two had slight local desquamation of the skin that was of irregular duration. At necropsy, no significant microscopic lesions were noted. Product formulations containing 5.0% (4.0 ml/kg doses) and 2.4% (227 mg/kg) Stearic Acid were applied daily to the shaved dorsal skin of female albino and female Sprague-Dawley rats, respectively, in 13-week dermal toxicity studies. Minimal to moderate skin irritation was noted during each study. An unspecified number of rats that received 5.0% Stearic Acid had subclinical bronchitis and "focal interstitial mononuclear cell infiltration into the kidneys, liver, and heart." In the same group, five of 15 rats had grade 1 hyperkeratosis. Minimal hyperkeratosis of the epidermis was observed in an unspecified number of rats given 2.4% Stearic Acid (Elder 1987).

In two separate studies, no signs of systemic toxicity were observed in rabbits that received topical applications of cosmetic formulations containing 4% Steareth-20 daily for 3 months. Slight to moderate dermal irritation occurred in both studies (Elder 1988).

Chronic Toxicity

Hamsters fed 5–15% PEG Monostearate for 28-39 weeks had high mortality, chronic diarrhea, atrophic testes, enlarged kidneys, thickened urinary bladder walls, striking hepatic, cecal, and splenic hemosiderosis, enlarged ceca, and obstructive nephropathy. Rats fed a diet containing 4% PEG-8 Stearate or 2% PEG-100 Stearate for 2 years had no treatment-related lesions over three successive generations (Elder 1983).

Toxic effects were not observed in groups of dogs fed 2% PEG-8, PEG-32, or PEG-75 for 1 year (Andersen 1993).

Anorexia, severe pulmonary infection, and high mortality were observed in rats fed 3000 ppm Stearic Acid for 30 weeks (Elder 1987).

Dermal Irritation

Skin irritation was slight when PEG Stearate compounds were tested at 100% concentrations in experimental test animals. PEG-2. -6, -8, -12, -20, -32, -40, and -150 Stearate were nonirritating in primary irritation patch tests using rabbits (Elder 1983).

The PEGs were not irritating to the skin of rabbits or guinea pigs. In irritation tests, undiluted PEG-6 was applied to the skin of rabbits for 4 hours and 50% PEG-75 was applied to the skin of guinea pigs for 4 days and to rabbits over a 13-week period (Andersen 1993).

In single insult occlusive patch tests for primary irritation, commercial grades of Stearic Acid, at doses of 35–65%, produced none to moderate erythema and slight, if any, edema in the skin of rabbits (Elder 1987).

In 24-hour patch tests, Steareth-2, -10, and -20 were either nonirritants or mild irritants when tested at concentrations up to 60% (Elder 1988).

Dermal Sensitization

PEG-2 Stearate (as a 0.1% suspension) was evaluated for dermal sensitization potential using guinea pigs and the Landsteiner and Jacobs sensitization procedure. Under the test conditions, PEG-2 Stearate was nonsensitizing. Likewise, PEG-8 and -40 Stearate were nonsensitizers (Elder 1983).

PEG-75 was not a sensitizer. In the guinea pig skin sensitization test, PEG-75 was tested at a concentration of 0.1% (Andersen 1993).

In maximization studies with two cosmetic product formulations containing 1 .O% Stearic Acid, slight reactions were observed to challenge patches. These formulations were considered weak, grade I, sensitizers. In another maximization study, after intradermal induction and booster injections of a formulation containing 3.5% Stearic Acid, reactions to topical challenge applications of the formulation were few and minimal in intensity. In guinea pig photosensitization studies, concentrations of up to 2.8% Stearic Acid in skin lotion formulations were not photoallergenic (Elder 1987).

Ocular Irritation

PEGs Stearate produced minimal ocular irritation when tested at concentrations up to 100% (Elder 1983).

PEG-6 and -75 did not cause cornea1 injuries when instilled (undiluted, 0.5 ml) into the conjunctival sac of rabbits. PEG-8 (35% solution, 0.1 ml) and PEG-32 (melted in water bath, 0.1 ml) induced mild ocular irritation in rabbits (Andersen 1993).

Stearic Acid alone, as well as cosmetic product formulations containing 1–65% Stearic Acid, produced no irritation or minimal irritation after single and multiple instillations into the conjunctival sac of rabbits. Irritation was primarily manifested as mild conjunctival erythema (Elder 1987).

Concentrations of 0.6–60% Steareth-2 were nonirritating or mildly irritating to the eyes of rabbits tested using a modified Draize procedure. Steareth- 10 (1 0–60%) was minimally irritating. Mild to moderate irritation and/or slight conjunctivitis were seen in rabbits tested with 1.5–60% Steareth-20 (Elder 1988).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Ethylene Glycol and its Ethers

It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers (e.g., methoxyethanol, a.k.a. ethylene glycol monomethyl ether) are reproductive and developmental toxins. The CIR Expert Panel undertook a separate, limited review of these compounds in order to assess the possibility that PEG-derived cosmetic ingredients could present similar concerns (CIR 1996). In summary, this report concluded that the ethylene glycol monoalkyl ethers are not themselves toxic, but rather that one or more alcohol or aldehyde dehydrogenase metabolites are toxic. From the available data, the report also concluded that the toxicity of the monoalkyl ethers is inversely proportional to the length of the alkyl chain (methyl is more toxic than ethyl than propyl than butyl, etc.).

Because of the methods of manufacture of the PEGs Distearate, the likelihood of methoxyethanol, ethoxyethanol, and other similar compounds being present as an impurities is slight to nil. In addition, because the PEG Distearate compounds are diesters of polyethylene glycol, and as such, are chemically different from alkyl ethers, the Panel concluded no reproductive or developmental hazards are posed by these compounds.

In multigenerational studies, rats fed diets containing 10–20% PEG-8 and -40 Stearate had decreased newborn litter survival time due to maternal neglect. Impairment of lactation efficiency as evidenced by lower weanling weights, greater mortality of nurslings, and decreased reproductive performance in the F3 generation were observed in rats fed diets containing 20% PEG-8 and -40 Stearate. No reproductive effects were noted in rats fed 5% PEGs Stearate (Elder 1983).

No adverse reproductive effects occurred during subchronic (90 days) and chronic (2 years) oral toxicity studies of PEG-6-32 and PEG-75. In the subchronic study, PEG-75 was tested at a dose of 0.23 g/kg/day. In the chronic study, PEG-75 was tested at doses up to 0.062 g/kg/day and PEG-6-32 at doses up to 1.69 g/kg/day (Andersen 1993).

MUTAGENICITY

PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test; the maximum test concentration in both studies was 1%. In the unscheduled DNA synthesis assay, a statistically significant increase in radioactive thymidine incorporation into rat hepatocyte nuclei was noted only at the highest concentration tested (0.1%). PEG- 150 was not mutagenic in the mouse lymphoma forward mutation assay when tested at concentrations up to 150 g/l (Andersen 1993).

Stearic Acid was inactive in aneuploidy induction tests (concentrations up to 500 μg/ml) and in the Ames test (50 μg/ml) with or without metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (Elder *1987).*

CARCINOGENICITY

All of the carcinogenicity data available on the PEGs was specifically on PEG-8, which was used as a solvent control for a number of studies. PEG-8 was not carcinogenic when administered orally to mice (30 weeks of dosing), intraperitoneally to rats (6 months of dosing), subcutaneously (20 weeks of dosing to rats; 1 year of dosing to mice), or when injected into the gastric antrum of guinea pigs over a period of 6 months (Andersen 1993).

No evidence of carcinogenicity was observed in studies of rats fed 0.3% or 50 g/kg/day Stearic Acid. In subcutaneous studies, a low incidence of carcinomas, sarcomas, and lymphomas was observed in mice receiving repeated subcutaneous injections of up to 82 mg Stearic Acid (Elder 1987).

CLINICAL STUDIES

Clinical studies of the PEGs Stearate indicate that these ingredients are neither irritants nor sensitizers, and no evidence of phototoxicity or photosensitization was observed in studies of the ingredient alone or in formulation. PEG-2 Stearate (25% aqueous) did not induce skin irritation or sensitization in a repeated-insult patch test (RIPT) involving 168 subjects. Neither photosensitization nor phototoxic reactions to PEG-2 Stearate were noted in a group of 28 subjects. Reactions also were not observed in 10 subjects patch tested (two 48-hours applications) with undiluted PEG- 100 Stearate, and the same was true for 188 subjects patch tested (RIPT) with a skin conditioner containing 1 to 3% PEG-100 Stearate. A skin conditioner containing 1 to 3% PEG- 100 Stearate also was not phototoxic to human subjects (Elder 1983).

In clinical studies, PEG-6 and PEG-8 induced mild sensitization in 9% and 4% of 23 male subjects tested, respectively. However, later production lots of PEG-6, as well as PEG-75, did not cause reactions in any of the 100 male and 100 female subjects tested. A product formulation containing 3% PEG-8 induced minimal to mild irritation (induction phase) in over 75% of 90 volunteers participating in a skin irritation and sensitization study. Responses (not classified) were noted in 22 subjects at the 24-hour challenge reading. Cases of systemic toxicity and contact dermatitis in bum patents were attributed to PEG-based topical ointments. The ointment that induced systemic toxicity contained 63% PEG-6, 5% PEG-20, and 32% PEG-75 (Andersen 1993).

Primary and cumulative irritation studies of up to 40% Stearic Acid in mineral oil were negative. Mild to intense erythema in single insult occlusive patch tests, soap chamber tests, and 2 1-day cumulative irritation studies were produced by cosmetic product formulations containing up to 13% Stearic Acid. These reactions were generally not related to the fatty acid concentrations in the formulations. In clinical repeated insult patch tests (open, occlusive, and semiocclusive), maximization tests, and prophetic patch tests with cosmetic product formulations containing up to 13% Stearic Acid, no primary or cumulative

irritation or sensitization was reported. A few subjects reacted to a few, isolated induction patches. Slight, if any, reactions were observed after challenge patching at original or adjacent sites on the upper backs or forearms of some subjects. Intensity of observed reactions to the formulations was not directly related to the concentrations of the fatty acid ingredients (Elder 1987).

Concentrations up to 60% Steareth-2, -10, and -20 were nonirritating and nonsensitizing in human single insult and repeated insult patch tests. Steareth-20 (4%) was not a cumulative irritant and did not induce contact photoallergenicity, contact dermatitis, or sensitization. A suntan formulation containing 2.75% Steareth-2 and 2.25% Steareth-20 was not phototoxic or photosensitizing (Elder 1988).

SUMMARY

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are the polyethylene glycol diesters of Stearic Acid. These ingredients are surfactants that function as emulsifying, cleansing, and solubilizing agents in cosmetics. Product formulation data submitted to the Food and Drug Administration (FDA) indicate that PEG-2, -3, -4, -6, -8, -12, -50, and -150 Distearate were in use, and that they were used in 283 cosmetic formulations.

Because few data on the PEGs Distearate regarding metabolism, toxicity, mutagenicity, carcinogenicity, and clinical safety were available, this review presented data on the PEGs, Stearic Acid, Steareths, and the PEGs Stearate separately, as these data were considered applicable to the safety evaluation of the PEGs Distearate.

PEG Distearate absorption and metabolism data were not available. PEG absorption is related to molecular weight. Lower molecular weight PEGs are readily absorbed through damaged skin. Oral and intravenous studies on PEGs indicate that these substances are excreted, unchanged, in the urine and feces. In general, fatty acids (such as Stearic Acid) are readily absorbed and distributed to the tissues in humans. Fatty acids can traverse the placental barrier.

Toxicity data for the PEGs Distearate were not available. The PEGs Stearate, and Steareths had low oral toxicity in acute, short-term, subchronic and chronic studies. PEGs in general have a low oral and dermal toxicity; the larger molecular weight PEGs appear to be less toxic than the smaller PEGs in oral studies. The acute toxicity of cosmetic formulations containing up to 13% Stearic Acid was low. In subchronic and chronic feeding studies using rats the effects were more severe.

PEG Stearates were slightly irritating at undiluted concentrations in test animals. PEGs were nonirritating to the skin of rabbits and guinea pigs, and PEG-75 was not a sensitizer. Stearic Acid irritation ranged from moderate to no reaction. Cosmetic product formulations containing 1 .O% Stearic Acid were weak, grade I sensitizers. Primary irritation and sensitization studies involving Stearic Acid and the PEGs Stearate were negative. Minimal ocular irritation occurred in tests with the PEGs, Stearic Acid, Steareths, and PEGs Stearate.

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, it was considered unlikely that the PEGs Distearate would cause reproductive or developmental effects based on their structural characteristics. In subchronic and chronic feed studies, PEG-6-32 and PEG-75 did not induce adverse reproductive effects in rats. In a multigenerational study lasting 2 years, feed containing 10–20% PEG-8 Stearate or PEG-40 Stearate was fed to rats; the rats fed the diet had decreased offspring survival time, reproductive performance, and lactation efficiency, as well as increased offspring mortality. Neither PEG-8 Stearate nor PEG-40 Stearate at a dietary concentration of 5% affected reproductive success.

In mutagenicity studies, PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test. At concentrations up to 150 g/l, PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay. Stearic Acid was not mutagenic in the Ames test. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to rodents. A low incidence of carcinomas, sarcomas, and lymphomas was evident in mice receiving multiple subcutaneous injections of Stearic Acid.

In clinical studies, PEG-8 was a mild sensitizer and irritant. Contact dermatitis and systemic toxicity in bum patients were attributed to a PEG-based topical ointment. The Steareths, PEGs Stearate, and Stearic Acid were not irritants, sensitizers, or phototoxins. Formulations containing Stearic Acid were not photosensitizing.

DISCUSSION

Safety test data on the PEGs Stearate polymers, the PEGs, Stearic Acid and the Steareths were all considered relevant and supportive of the safety of the PEGs Distearate polymers. The CIR Expert Panel was concerned about the sensitization and toxicity potential of the PEGs Distearate when applied to damaged skin. This concern arose because of positive patch tests and incidences of nephrotoxicity in bum patients treated with an antimicrobial cream that contained PEG-6, PEG-20, and PEG-75. PEG was the causative agent in both animal and human studies; no evidence of systemic toxicity or sensitization was found in studies with intact skin. The Expert Panel concluded that cosmetic formulations containing PEGs should not, therefore, be used on damaged skin.

Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. They stressed that the cosmetics industry should continue to use the necessary procedures to remove these impurities from the PEG Distearate ingredients before blending them into cosmetic formulations. Based on particle size and cosmetic use concentrations, it was not considered likely that these ingredients, in formulation, are respirable. Thus, the Expert Panel had no concerns regarding the absence of inhalation toxicity data, and the Panel considers the PEGs Distearate safe for use in aerosolized products.

As discussed earlier in this report, the possibility of reproductive and developmental effects was determined not to be of concern.

CONCLUSION

The CIR Expert Panel concludes that PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are safe for use in cosmetic formulations under the present practices of use.

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Final Report on the Safety Assessment of PEG (Polyethylene Glycol)-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE[1]

PEGs Dilaurate and PEGs Laurate are the diesters and monoesters, respectively, of polyethylene glycol and lauric acid used in a wide variety of cosmetic formulations as surfactants—emulsifying agents. PEG esters are produced by the ethoxylation of fatty acids. In general, ethoxylated fatty acids can contain 1,4-dioxane as a by-product of ethoxylation. Traces of the reactants (fatty acid, ethylene oxide, and any catalysts) may remain in the finished product. Current concentration of use data were not available; the highest previously reported concentration was 25%. The PEGs Dilaurate and PEGs Laurate are similar to the PEGs Stearate and PEGs Distearate, and to the components (Polyethylene Glycol and Lauric Acid); all of which have been addressed in previous safety assessments. PEGs were readily absorbed through damaged skin. Fatty acids such as Lauric Acid are absorbed, digested, and transported in animals and humans. The acute oral LD_{50} of PEG-12 Laurate was >25 g/kg in mice. In short-term feeding studies, PEGs Laurate were irritating to the gastrointestinal tract, but not necrotizing. In chronic oral toxicity studies, there was some evidence of liver damage and hyperplasia in several tissues. It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers are reproductive and developmental toxins. These esters and diesters are chemically different from PEG alkyl ethers and are not expected to cause adverse reproductive or developmental effects. In actual studies, PEGs Stearate, and PEGs Distearate did not cause reproductive or developmental toxicity, and were not carcinogenic. Likewise, PEGs were not carcinogenic. Although sensitization and nephrotoxicity were observed in burn patients treated with a PEG-based cream, no evidence of systemic toxicity or sensitization was found in studies with intact skin. Because of the possible presence of 1,4-dioxane reaction product and unreacted ethylene oxide residues, it was considered necessary to use appropriate procedures to remove these from PEGs Dilaurate and PEGs Laurate ingredients before blending them into cosmetic formulations. Based on the limited data on the PEGs Dilaurate and the PEGs Laurate, on the data available on the component ingredients, and on the data available on similar PEG fatty acid esters, it was concluded that PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEG-2, -4, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE are safe for use in cosmetics at concentrations up to 25%.

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INTRODUCTION

Polyethylene Glycol (PEG)-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate and PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150 and -200 Laurate are PEG diesters or esters of lauric acid that serve as surfactants—emulsifying agent or surfactants—cleaning agents in cosmetic product formulations. PEG-2 Laurate SE is a self-emulsifying grade of PEG-2 Laurate that contains some sodium and/or potassium laurate; PEG-2 Laurate SE is used as a surfactant—emulsifying agent in cosmetic product formulations.

The PEGs Dilaurate and PEGs Laurate are similar to the PEGs Stearate and PEGs Distearate, and to the components (Polyethylene Glycol and Lauric Acid), all of which have been addressed in previous safety assessments. The conclusions reached in those earlier assessments are described below.

PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates are safe as cosmetic ingredients in the present practices of concentration and use (Elder 1983a).

PEG-2, -3, -4, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are safe for use in cosmetic formulations in the present practices of use (CIR 1996).

PEG-6, -8, -32, -75, -150, -14M, and -20M are safe for use at the concentrations reflected in the Cosmetic Use section and in the product formulation safety test data included in the Final Report. The Expert Panel recommends that cosmetic formulations containing these PEGs not be used on damaged skin (Andersen 1993).

Laureth-4 and -23 (polyethylene glycol ethers of lauryl alcohol) are safe as cosmetic ingredients in the present practices of use and concentration (Elder 1983b).

Lauric Acid is safe for use as a cosmetic ingredient (Elder 1987).

Because there are limited data available to address the safety of PEGs Dilaurate and PEGs Laurate, and because the PEGs Dilaurate and PEGs Laurate are similar to the PEGs Stearate and

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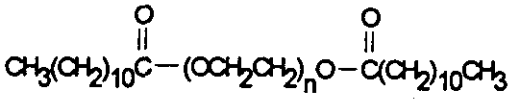

FIGURE 1
PEG-n Dilaurate.

PEGs Distearate, and to the components (Polyethylene Glycol and Lauric Acid), the relevant data from the previous safety assessments have been summarized in this review as a further basis for the assessment of safety of the PEGs Dilaurate and PEGs Laurate.

CHEMISTRY

Definition and Structure

The PEGs Dilaurate (generic CAS No. 9005-02-1) are polyethylene glycol diesters of lauric acid (coconut-derived) that conform generally to the formula in Figure 1, where *n* has an average value equal to the number in the name. PEG-n Dilaurate is also known as Polyoxyethylene (*n*) Dilaurate. Synonyms for PEG-2 Dilaurate are Polyethylene Glycol (100) Dilaurate; Dodecanoic Acid, Oxydi-2,1-Ethanediyl Ester; and Oxydi-2,1-Ethanediyl Dodecanoate. PEG-4 Dilaurate is known as Polyethylene Glycol 200 Dilaurate. PEG-6 Dilaurate is called Polyethylene Glycol 300 Dilaurate. Synonyms for PEGs-8 and -12 Dilaurate are Polyethylene Glycol 400 Dilaurate and Polyethylene Glycol 600 Dilaurate, respectively. Other names for the remaining PEGs Dilaurate are Polyethylene Glycol 1000 Dilaurate(-20), Polyethylene Glycol 1540 Dilaurate(-32), Polyethylene Glycol 4000 Dilaurate(-75), and Polyethylene Glycol 6000 Dilaurate(-150) (Wenninger, Canterbery, and McEwen 2000).

The PEGs Laurate (generic CAS No. 9004-81-3) conform generally to the structure in Figure 2, where *n* has an average value equal to the number in the name. A general synonym for the PEGs Laurate is Polyoxyethylene (*n*) Monolaurate. PEG-2 Laurate is also known as Diethylene Glycol Monolaurate; Diglycol Laurate; Diglycol Monolaurate; Dodecanoic Acid, 2-(2-Hydroxyethoxy)Ethyl Ester; and Polyethylene Glycol 100 Monolaurate. Synonyms for PEG-4 Laurate are Dodecanoic Acid, 2-[2-(2-Hydroxyethoxy)Ethoxy]Ethyl Ester; 2-[2-[-2(2-Hydroxyethoxy)Ethoxy]Ethoxy]Ethyl Dodecanoate; and Polyethylene Glycol 200 Monolaurate. Other names for PEG-6 Laurate are Dodecanoic Acid, 17-Hydroxy-3,6,9,12,15-Pentaoxaheptadec-1-yl Ester; 17-Hydroxy-3,6,9,12,15-Pentaoxaheptadec-1-yl Dodecanoate; and Polyethylene Glycol 300 Monolaurate. PEG-8 Laurate is also known as Dodecanoic Acid,

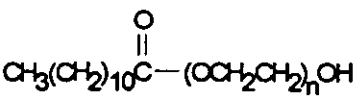

FIGURE 2
PEG-n Laurate.

23-Hydroxy-3,6,9,12,15,18,21-Heptaoxatricos-1-yl Ester; 23-Hydroxy-3,6,9,12,15,18,21-Heptaoxatricos-1-yl Dodecanoate; and Polyethylene Glycol 400 Monolaurate. PEG-9, -10, -12, -20, -32, -75, and -150 Laurate are also known as Polyethylene Glycol 450 Monolaurate; Polyethylene Glycol 500 Monolaurate; Polyethylene Glycol 600 Monolaurate; Polyethylene Glycol 1000 Monolaurate; Polyethylene Glycol 1540 Monolaurate; Polyethylene Glycol 4000 Monolaurate; Polyethylene Glycol 6000 Monolaurte, respectively. A synonym for PEG-14 Laurate is Polyethylene Glycol (14) Monolaurate (Wenninger, Canterbery, and McEwen 2000).

PEG-2 Laurate SE is a self-emulsifying grade of PEG-2 Laurate that contains sodium and/or potassium laurate. Other names for this compound are Polyethylene Glycol 100 Monolaurate Self-Emulsifying and Polyoxyethylene (2) Monolaurate Self-Emulsifying (Wenninger, Canterbery, and McEwen 2000).

Chemical and Physical Properties

The chemical and physical properties of PEG-4, -8, and -150 Dilaurate are described in Table 1, and the properties of PEG-2, -4, -8, and -12 Laurate are described in Table 2.

Impurities

PEG-n Laurate contains unspecified amounts of lauric acid diester of PEG and unreacted PEG (Yakuji Nippo 1979).

Silverstein et al. (1984) reported that PEG-6 may contain small amounts of monomer and dimers. The amounts were not quantified.

Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75 (Hamburger, Azaz, and Donbrow 1975). The amount of peroxide in PEGs is dependent upon the molecular weight of the PEG and its age. The older the compound, the greater the concentration of peroxides. In a colorimetric assay used to determine the peroxide concentrations in several production lots of PEGs, PEG-6 and PEG-8 were each added to acidified potassium iodide solution, and the iodine liberated was titrated against a standard thiosulfate solution. PEG-6 had peroxide concentrations ranging from 1.4 to 9.3 μEq thiosulfate/ml glycol. PEG-8 had concentrations ranging from 3.24 to 5.7 μEq thiosulfate/ml glycol. The specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide (McGinity, Hill, and La Via 1975).

Ethoxylated surfactants may also contain 1,4-dioxane, a by-product of ethoxylation (Robinson and Ciurczak 1980). 1,4-Dioxane is a known animal carcinogen (Kociba et al. 1974; Hoch-Ligeti, Argus, and Arcos 1970; Argus, Arcos, and Hoch-Ligeti 1965). In the Cosmetic Ingredient Review (CIR) safety assessment of the PEG Stearates, the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations. Traces

TABLE 1
Chemical and physical properties of PEGs Dilaurate

Property	Description	Reference
PEG-4 Dilaurate		
Appearance	Pale yellow, viscous (oily) liquid	Nikitakis and McEwen 1990a
Solubility	Soluble in mineral oil, triolein, methyl alcohol, acetone, ethyl alcohol, ethyl acetate, toluol, vegetable oil and isopropyl alcohol; dispersible in water, isopropyl myristate, and glycerin	Nikitakis and McEwen 1990a
	When hot, completely soluble in naphtha and mineral oil; when cold, miscible in certain proportions in naphtha and poorly soluble in mineral oil	Glyco Chemicals, Inc. No date
Acid value	8.0 max.	Nikitakis and McEwen 1990a
Hydroxyl value	20–40	Nikitakis and McEwen 1990a
Saponification value	180–190	Nikitakis and McEwen 1990a
Iodine value	3.0 max.	Nikitakis and McEwen 1990a
Specific gravity at 25°C	0.96	Glyco Chemicals, Inc. No date
Melting point or solidification point (°C)	<14	Glyco Chemicals, Inc. No date
pH of 5% aqueous dispersion	4.0–5.0	Glyco Chemicals, Inc. No date
Moisture	0.5% max.	Nikitakis and McEwen 1990a
PEG-6 Dilaurate		
HLB value	6.3	Cosmetic Science & Technology On-line 1997
PEG-8 Dilaurate		
Appearance	Clear, pale yellow liquid with a slightly fatty odor	Nikitakis and McEwen 1990b
Solubility	Soluble in isopropyl alcohol, methyl alcohol, ethyl alcohol, acetone, ethyl acetate, toluol, naphtha, mineral oil, vegetable oil, and toluene	Glyco Chemicals, Inc. No date
	Soluble in isopropanol and toluene and dispersible in water	Nikitakis and McEwen 1990b
Specific gravity at 25/25°C	0.985–0.995	Nikitakis and McEwen 1990b
pH of 5% aqueous dispersion	3.0–6.0	Nikitakis and McEwen 1990b
Acid value	10.0 max.	Nikitakis and McEwen 1990b
Saponification value	125–137	Nikitakis and McEwen 1990b
Iodine value	10.0 max.	Nikitakis and McEwen 1990b
HLB value	10.4	Cosmetic Science & Technology On-line 1997
Melting point or solidification point (°C)	<15	Glyco Chemical Inc. No date
PEG-150 Dilaurate		
Physical properties	Tan, waxy solid with a slightly fatty odor	Nikitakis and McEwen 1990b
Solubility	Soluble in isopropanol, toluene, and water	Nikitakis and McEwen 1990b
Melting range	53–60°C	Nikitakis and McEwen 1990b
Acid value	9.0 max.	Nikitakis and McEwen 1990b
Saponification value	14–22	Nikitakis and McEwen 1990b
Iodine value	1.5 max.	Nikitakis and McEwen 1990b

TABLE 2
Chemical and physical properties of PEGs Laurate

Property	Description	Reference
PEG-2 Laurate		
Appearance	Light yellow, oily liquid	Nikitakis and McEwen 1990b
Solubility	Soluble in alcohol and mineral oil; dispersible in water	Nikitakis and McEwen 1990b
Specific gravity at 25°/25°C	0.97–0.99	Nikitakis and McEwen 1990b
pH of 5% aqueous solution	8.4–9.4	Nikitakis and McEwen 1990b
Acid value	6.0 max.	Nikitakis and McEwen 1990b
Saponification value	165–175	Nikitakis and McEwen 1990b
Iodine value	10 max.	Nikitakis and McEwen 1990b
PEG-4 Laurate		
Physical properties	Light yellow, oily liquid with a "typical odor"	Nikitakis and McEwen 1990b
Solubility	Soluble in ethanol; insoluble in mineral oil; dispersible in water	Nikitakis and McEwen 1990b
pH of 5% aqueous dispersion	3.0–5.0	Nikitakis and McEwen 1990b
Acid value	5.0 max.	Nikitakis and McEwen 1990b
Saponification value	130–135	Nikitakis and McEwen 1990b
Hydroxyl value	134–144	Nikitakis and McEwen 1990b
Iodine value	9.5 max.	Nikitakis and McEwen 1990b
PEG-8 Laurate		
Appearance	Light yellow, oily liquid with a "characteristic odor"	Glyco Chemicals, Inc. No date
Solubility	Soluble in water and ethanol; insoluble in mineral oil	Nikitakis and McEwen 1990b
Specific gravity at 25°/25°C	1.025–1.040	Nikitakis and McEwen 1990b
pH of 10% aqueous solution	3.0–6.5	Nikitakis and McEwen 1990b
Acid value	5.0 max.	Nikitakis and McEwen 1990b
HLB value	13.1	Cosmetic Science & Technology On-line 1997
Saponification value	86–105	Nikitakis and McEwen 1990b
Iodine value	5.0 max. (<8)	Nikitakis and McEwen 1990b
Melting point (°C)	<8	Glyco Chemicals, Inc. No date
Moisture	1.0% max.	Nikitakis and McEwen 1990b
PEG-12 Laurate		
Appearance	Light yellow liquid at 25°C	Nikitakis and McEwen 1990b
Solubility	Soluble in water and ethanol; insoluble in mineral oil	Nikitakis and McEwen 1990b
pH of 3% aqueous solution	4.2–4.8	Nikitakis and McEwen 1990b
pH of 5% aqueous dispersion	6.0–8.0	Glyco Chemicals, Inc. No date
Specific gravity at 25°/25°C	1.01	Glyco Chemicals, Inc. No date
Melting point (°C)	20–25	Glyco Chemicals, Inc. No date
Acid value	5.0 max. (<6)	Nikitakis and McEwen 1990b
Saponification value	66–80	Nikitakis and McEwen 1990b
Iodine value	5.0 max. (<8)	Nikitakis and McEwen 1990b
Moisture	1.0% max.	Nikitakis and McEwen 1990b
PEG-20 Laurate		
HLB value	16.5	Cosmetic Science & Technology On-line 1997

of the reactants, stearic acid, ethylene oxide, and the catalytic agents used, may remain in the finished product (Elder 1983a, 1983b).

Reactivity

PEGs Stearate are relatively stable compounds; however, the ether oxygens are potentially reactive and the ester bonds are potentially vulnerable to enzymatic cleavage (Elder 1983a).

Method of Manufacture

In general, polyoxyethylene ester emulsifiers and surfactants are produced using the ethoxylation of fatty acids such as lauric acid and stearic acid. Two modes of reaction between alkylene oxides and fatty acids can occur: uncatalyzed and alkali catalyzed. The uncatalyzed addition is a slow reaction, which involves alkoxylation, esterification, and alkylene oxide hydrolysis. The alkali-catalyzed ethoxylation is more complex, and involves interesterification. No significant chain lengthening with ethylene oxide occurs until complete formation of the glycol monoester has been achieved (Swern 1979).

PEG-2 Laurate is produced by an interesterification reaction of coconut oil with diethylene glycol (Nikitakis and McEwen 1990b).

USE

Cosmetic

The PEGs Dilaurate function as surfactants—emulsifying agents in cosmetic formulations. PEG-75 Dilaurate and PEG-150 Dilaurate also serve as surfactants-solubilizing agents (Wenninger, Canterbery, and McEwen 2000). Data submitted to the Food and Drug Administration (FDA) in 1996 indicated that PEG-8 and -12 Dilaurate were used in 40 cosmetic formulations, and PEG-2, -4, -8, -10, -15, and -200 Laurate were used in 20 formulations (Table 3). PEG-2, -6, -12, -20, -32, -75, and -150 Dilaurate, PEG-2 Laurate SE, and PEG-6, -9, -12, -14, -20, -32, -75, and -150 Laurate had no reports of use (FDA 1996).

Current concentration of use data are not available from industry, but historical data are available (FDA 1984). In 1984, PEG-4 Dilaurate was used at concentrations of 1% to 25% (mostly 5%–10%), and PEG-8 Dilaurate was used at concentrations of 0.1% to 25%. PEG-2 Laurate was used at concentrations of 0.1% to 10% (mostly 0.1%–1%). PEG-2 Laurate SE and PEG-9 Laurate were used at unknown concentrations. PEG-4 Laurate was used at concentrations of 0.1% to 25% (mostly 0.1% to 1%). The concentrations of use of PEG-8 Laurate ranged from 0.1% to 10% (mostly 1%–5%). PEG-12 Laurate was used at 5% to 10%.

Noncosmetic

The PEGs Dilaurate are indirect food additives that are used in resinous and polymeric coatings, paper and/or paperboard, and textiles and/or textile fibers as described in the Code of Federal Regulations (CFR) in 21CFR 175.105, 175.300, 176.170, 176.180, 176.200, 176.210, 177.1210, 177.2260, 177.2800, and 178.3520 (CFR 1992).

PEG-8 Dilaurate is used as a plasticizer for vinyls. PEG-12 Laurate is used as a liquid nonionic detergent for woolens, dishes, and other items. PEG-8 Laurate is used as an antistatic agent in weaving nylon and saran, as an ingredient in latex emulson paints, as an emulsifier for solvents and oils, as a dye assistant and penetrating agent for dyeing cotton and rayon, and as a nonionic wetting agent (Glyco Chemicals, Inc. No date).

GENERAL BIOLOGY

Absorption, Metabolism, Distribution, and Excretion

PEGs Stearate

PEG-40 Stearate is hydrolyzed in vitro by pancreatic lipase. When the same compound was hydrolyzed with alkali, a 5 to 1000 mg percent concentration range of the polyoxyethylene hydrolysate had no hemolytic effect on defibrinated human blood tested at 37°C for 18-hours: PEG-40 Stearate also produced no significant interference with oxygen uptake by kidney tissue preparations. PEG-20, -30, and -40 Stearate activated the cytochrome oxidase enzyme system in heart muscle preparations up to a concentration of 150 mg/ml (Elder 1983a).

Polyethylene Glycol

Gastrointestinal absorption of PEGs is dependent on the molecular weight of the compound. In general, the greater the molecular weight of the PEG compound, the lesser the absorption that occurs. In both oral and intravenous (IV) studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and feces. In a study with human burn patients, monomeric ethylene glycol was isolated in the serum following topical exposure to a PEG-based antimicrobial cream, indicating that PEGs are readily absorbed through damaged skin (Andersen 1993).

Lauric Acid

In general, fatty acids such as stearic acid are absorbed, digested, and transported in animals and humans. Radioactivity from labeled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph. β-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl coenzyme A (CoA). Placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied. High intake of dietary saturated fatty acids has been associated with increased incidence of atherosclerosis and thrombosis. Fatty acids are typically transported esterified to glycerol in chylomicrons and very low density lipoproteins. Lauric Acid is transported via the lymphatic and (as a free fatty acid) portal systems. Lauric Acid inhibited the growth of various microorganisms, including bacteria and fungi, and inactivated enveloped viruses such as herpes, influenza, Sendai, and Sindbis viruses. The minimal inhibitory concentrations (at 37°C)

TABLE 3
Frequency of use of PEGs Dilaurate and PEGs Laurate (FDA 1996)

Product category (Number of Formulations Reported to FDA)	Number of formulations containing ingredient
PEG-4 Dilaurate	
Bath oils, tablets, and salts (147)	9
Other fragrance preparations (195)	1
Aftershave lotion (268)	1
Cleansing preparations (820)	1
Body and hand (excluding shaving) preparations (1012)	1
Moisturizing preparations (942)	1
Other skin care preparations (810)	1
1996 Total for PEG-4 Dilaurate	**15**
PEG-8 Dilaurate	
Bath oils, tablets, and salts (147)	7
Hair conditioners (715)	5
Shampoos (Noncoloring) (972)	1
Tonics, dressings, and other hair grooming aids (604)	7
Cuticle softeners (26)	1
Cleansing preparations (820)	3
Other skin care preparations (810)	1
1996 Total for PEG-8 Dilaurate	**25**
PEG-2 Laurate	
Body and hand (excluding shaving) (1012)	1
1996 Total for PEG-2 Laurate	**1**
PEG-4 Laurate	
Cuticle softeners (26)	1
Cleansing (820)	3
Face and neck (excluding shaving) (300)	1
1996 Total for PEG-4 Laurate	**5**
PEG-8 Laurate	
Permanent waves (434)	1
Tonics, dressings, and other hair grooming aids (604)	1
Other hair preparations (395)	1
Cleansing (820)	1
Body and hand (excluding shaving) (1012)	1
Other skin care preparations (810)	1
Suntan gels, creams, and liquids (196)	1
Indoor tanning preparations (67)	1
Other sutan preparations (68)	1
1996 Total for PEG-8 Laurate	**9**
PEG-10 Laurate	
Shampoos (Noncloring) (972)	2
1996 Total for PEG-10 Laurate	**2**
PEG-15 Laurate	
Indoor tanning preparations (67)	2
1996 Total for PEG-15 Laurate	**2**
PEG-200 Laurate	
Shaving cream (158)	1
1996 Total for PEG-200 Laurate	**1**

of Lauric Acid ranged from 0.062 mM (*Streptococcus pneumoniae*) to 4 mM (*Candida utilis*) (Elder 1987).

Miscellaneous Effects

The deposition of the germicide trichlorocarbanilide (TCC) on the skin was enhanced in the presence of both PEG-8 Laurate and sodium chloride (Elkhouly and Woodroffe 1970, 1973). The antibacterial activity of TCC/PEG-8 Laurate systems was also increased when 0.5% sodium chloride was added.

ANIMAL TOXICOLOGY

Acute Toxicity

Laureths

The acute oral LD_{50} of Laureths was between 4.9 and 9.1 g/kg in rats and mice, between 5 and 10 g/kg in Swiss mice, and >25 g/kg in rats (Elder 1983b).

PEGs Laurate

The acute oral LD_{50} of PEG-12 Laurate was >25 g/kg and the intravenous LD_{50} was 500 mg/kg in Harlan albino mice (Hopper, Hulpieu, and Cole 1949).

PEGs Distearate

Hopper, Hulpieu, and Cole (1949) reported the toxicological properties of several surface-active agents, including PEG-8 and PEG-20 Distearate. The LD_{50} values for those two compounds were 365 mg/kg and 220 mg/kg, respectively, when administered intravenously to albino Harlan mice weighing between 14 and 23 g.

PEGs Stearate

The acute oral LD_{50} values of 50% PEG-2-150 Stearate (in corn oil unless specified) were each determined using rats. The LD_{50} values were >10 g/kg for PEG-2 Stearate; >10 g/kg (in corn oil) and >31.6 g/kg (aqueous) for PEG-8 Stearate; >10 g/kg for PEG-12 Stearate; >10 g/kg and 19.9 g/kg for PEG-20

Stearate; >10 g/kg for PEG-32 Stearate; 32 g/kg for PEG-40 Stearate (vehicle not specified); >25 g/kg for aqueous solutions of both PEG-50 and -100 Stearate; and >10 g/kg for PEG-150 Stearate. The acute oral LD_{50} of hair cream preparation containing 1.5% PEG-6 Stearate was >34.6 g/kg in rats. The acute intraperitoneal (IP) LD_{50} of PEG-8 Stearate was >9 ml/kg in rats given 2-ml injections. No signs of toxicity were observed in rats given IP injections of 2.5 g/kg PEG-50 Stearate or PEG-100 Stearate. A concentration of 5% PEG-40 Stearate given as a 5-ml injection into the lumen of the jejunum of a dog had no effect on blood pressure. That same day, an IV injection produced a prolonged hypotensive response. It was stated that this response was a "characteristic reaction" of the dog to a variety of polyoxyethylene compounds. The acute dermal LD_{50} of 15% PEG-8 Stearate was >10 ml/kg in rabbits; the only effect noted was moderate erythema at the application sites at 24 hours which cleared by day 3 (Elder 1983a).

Polyethylene Glycol

Acute oral LD_{50} values for PEGs in rabbits were 17.3 g/kg (100% PEG-6) and 76 g/kg (100% PEG-75). In acute dermal studies, no deaths were reported in groups of rabbits dosed with 20 ml/kg of either undiluted PEG-6 or 40% PEG-20M (Andersen 1993).

Lauric Acid

Male albino rats (five per group) were given 0.464 to 10.0 g/kg Lauric Acid in order to determine the acute oral toxicity of the fatty acid. Rats treated with 4.64 g/kg and 10.0 g/kg Lauric Acid had transient signs of toxicity. Slight depression, depressed righting and placement reflexes, oily and unkempt fur, mucoid diarrhea, excessive salivation, and serosanguineous discharge from the nose and eyes were observed. One rat given 10.0 g/kg Lauric Acid died 1 day after treatment; this rat had congested lungs and kidneys, and advanced autolytic changes.

A product formulation containing 8.7% Lauric Acid was administered to five albino rats as a 5-g/kg oral dose. No signs of toxicity were observed (Elder 1987).

Short-Term Toxicity

PEGs Laurate

Ringrose and Waller (1959) fed male New Hampshire cockerel chicks PEG-4, -8, and -20 Laurate for 10 weeks. In one study, 192 chicks (12 per group) were fed 0.1% or 1.0% PEG-20 Laurate. In the second study, 400 chicks (10 per group) were given 0.1%, 1.0%, or 2.0% PEG-4 or -8 Laurate. Chicks fed the PEGs Laurate were normal with respect to mortality, diarrhea, growth, gross findings, and flavor, as compared to chicks of the control group.

PEGs Laurate and PEGs Stearate

Male weanling Sprague-Dawley rats (13 per group) were fed a diet containing 25% PEG-20 Laurate or PEG-8 Stearate for 59 days (Harris et al. 1951). Rats of the control group ($n = 13$) were given feed containing hydrogenated oils (Crisco). The rats were weighed twice weekly and observed daily for changes in gross appearance and/or activity. For rats given PEG-20 Laurate, the mean weight gain/rat was 74 g, and the weight of feed consumed was 15.9 g/rat/day. For rats given PEG-8 Stearate, the mean weight gain/rat was 88 g, and the weight of feed consumed was 13.4 g/rat/day. In order to determine whether the compounds affected the rate of blood clotting, the blood-clotting time was measured on days 14 and 42 using several rats taken from random from each group. On day 59, the animals were decapitated and examined for gross lesions.

No changes in the rate of blood clotting were observed in rats of any treatment group. Rats of the control group had no signs of toxicity. All rats given PEG-20 Laurate had diarrhea, but inflammation of the anal region was not as severe as in rats given PEG-20 Sorbitan Laurate. In several instances, blood clots in the anorectal region were observed at necropsy. A few of the rats improved somewhat during the second half of the study. The rats gained weight continually after the third day, but their weight gain was somewhat less than that of rats given PEG-8 Stearate; this weight gain reduction suggested that the laurate compound was more harmful than the stearate. One rat died before scheduled necropsy, and three rats had bladder stones, which were tentatively identified as oxalate crystals.

Rats given PEG-8 Stearate had neither hemorrhage nor diarrhea, their fur was sleek and tidy, and they appeared normal throughout the study. The rats had an initial loss in weight, but gained weight consistently after day 3. The weight increase was lower in rats of this group than in rats of the control group.

The investigators also fed PEG-20 Laurate and PEG-8 Stearate to Sprague-Dawley rats (14 male and 16 female) for 70 days. The beginning test concentration of 5% was sequentially increased to 10%, 15%, and 25% during the first 10 days of the study; this procedure was used to reduce the shock from a sudden feeding of large amounts of the test substances. The rats were weighed and observed as above, and were killed by decapitation on day 70.

The rats fed PEG-20 Laurate had diarrhea within 2 weeks of feeding. The severity of the diarrhea increased until the anal region of most rats was highly inflamed. The mean weight gains per rat were 210 g (male) and 121 g (female). The mean weight of feed consumed was 12.7 g/rat/day. The mean weight gain of rats in this group was 62% of that of rats of the control group (hydrogenated oils); the mean weight gains per rat were 98 g (male) and 62 g (female). The mean weight of feed consumed by rats of the control group was 5.7 g/rat/day. Rats given PEG-8 Stearate had no gross signs of toxicity except that growth was 67% of that of the control rats.

Organ weights of rats fed either PEG-20 Laurate or PEG-8 Stearate did not differ from those of controls. All of the test substances were irritating to the gastrointestinal tract, but not necrotizing, as compared to the control substance. The cortical tubules of the kidneys had mild degeneration (probably reversible), and stains for fat were negative. Significant hepatic

changes were not observed. In the spleen of treated rats, giant cells were noted more frequently than in the spleen of control rats. These cells were presumably of monocyte/macrophage origin. Monocyte/macrophage hyperplasia was also observed. Males given the test substances had areas of incomplete maturation in the testes; findings in the ovaries of females were inconclusive. Rats of all groups had thickening of the alveolar wall by chronic inflammation cells (pneumonitis), but these changes were more frequent and prominent in rats given the test substances.

PEGs Stearate

Weanling hamsters fed a diet containing 5% or 15% PEG Monostearate for 2 to 10 weeks had severe lesions in the duodenum, ileum, liver, kidneys, and testes. Severe erosion of the ileal mucosa and necrosis of the liver were observed. Spermatogenic activity was decreased and tubular degeneration occurred in the kidneys. No signs of toxicity were observed in rats, monkeys, mice, and dogs fed diets containing up to 4% PEG-8, -40, -50, or -100 Stearate. Rabbits exposed topically for 20 days to 0.5 to 2.0 g/kg of 1.5% PEG-6 Stearate in a product formulation had erythema, dryness, wrinkling, desquamation, and hyperkeratosis at the application sites. No other signs of toxicity were noted (Elder 1983a).

Polyethylene Glycol

No toxicity was reported in rabbits that received daily topical applications of PEG-20M (0.8 g/kg/day) for 30 days. The only effect noted in the study was transient, mild erythema. The only evidence of systemic toxicity that resulted from dermal exposure was noted in rabbits that received repeated applications of an antimicrobial cream containing 63% PEG-6, 5% PEG-20, and 32% PEG-75 to excised skin sites for seven days (Andersen 1993).

Lauric Acid

The follicular-keratogenic properties of Lauric Acid were studied after topical application to the skin of the external ear canal of four albino rabbits. Lauric Acid (~18 mmol % in alcohol) was applied daily, 5 days per week for 6 weeks, as a 3-ml test volume. Rabbits of the control groups received either no treatment or absolute alcohol. Rabbits given Lauric Acid had erythema on the second day of treatment. The intensity of the observed redness increased over the next few days, and desquamation developed. Distinct follicular keratosis was observed within 1 month. After discontinuation of the applications, the erythema and scaling gradually disappeared, but the keratosis persisted after the 6-week treatment period had ended (Elder 1987).

Subchronic Toxicity

Laureths

Rabbits were treated topically with 0.4 ml/kg/day of Laureth-4 at 6% in a 52% ethanol/water solution for 21 days. Epidermal acanthosis in the animals was attributed to the alcohol (Elder 1983b).

PEGs Stearate

Six large calculi (4–6 mm in diameter; 50–95 mg in weight) were found in the urinary bladders of hamsters fed unspecified PEGs Stearate for 74 to 260 days. Rabbits fed a diet containing 4% PEG-8 Stearate for four months or 5% PEG-8 Stearate for 19 weeks had no treatment-related effects (Elder 1983a).

Polyethylene Glycol

In subchronic, 90-day toxicity studies involving groups of albino rats, the largest (PEG-20M) and smallest (PEG-6) molecular weight PEGs tested did not induce toxicity or death when administered daily in the diet or drinking water, respectively, at concentrations of 4% or less. No evidence of toxicity was observed in rabbits that received topical applications of 2 ml/kg/day of PEG-6 daily, 5 days/week, for 18 weeks (Andersen 1993).

Chronic Toxicity

Laureths

Rabbits were treated topically with 0.4 ml/kg/day of Laureth-4 at 6% in a 52% ethanol/water solution daily for 3 months. Edema, erythema, and eschar formation, hyperkeratosis, acanthosis, and dermatitis in the animals was attributed to the alcohol (Elder 1983b).

PEGs Dilaurate

Nine Sprague-Dawley rats were fed 6% PEG-8 Dilaurate for 505 days to determine the compound's chronic toxicity (Krehl, Cogwell, and Whedon 1955). PEG-8 Dilaurate was added to the basal diet in lieu of lard, which was present in the feed given to 9 rats of the control group. Feed consumption was greater in rats given PEG-8 Dilaurate than in rats of the control group, but this was not considered significant. Four rats fed PEG-8 Dilaurate died, and four rats of the control group also died. The remaining rats were killed at the end of the experimental period, and the spleen, liver, lungs, testes, thyroid gland, adrenal glands, kidneys, intestines, urinary bladder, heart vessels, and heart muscle were removed, weighed, and prepared for gross and microscopic examinations. One rat had cystic spots on the liver, one rat had hemorrhagic lungs, and one had a large neoplasm (fibrosarcoma, weight = 128.6 g). At microscopic examination, focal parenchymal hepatitis was observed in three rats of the test group.

PEGs Stearate

Hamsters fed 5% to 15% PEG Monostearate for 28 to 39 weeks had high mortality, chronic diarrhea, atrophic testes, enlarged kidneys, thickened urinary bladder walls, striking hepatic, cecal, and splenic hemosiderosis, enlarged ceca, and obstructive nephropathy. Rats fed a diet containing 4% PEG-8 Stearate or 2% PEG-100 Stearate for 2 years had no treatment-related lesions over 3 successive generations (Elder 1983).

PEG-20 Laurate and Lauric Acid

The oral toxicities of PEG-20 Laurate and lauric acid were evaluated for up to 2 years using Osborne-Mendel albino rats

(Fitzhugh, Schouboe, and Nelson 1960). Five male rats were fed 10% lauric acid for 18 weeks, and five rats of the control group were fed a basal diet. Neither clinical signs of toxicity nor adverse effects on weight gain were observed. None of the rats of either the control group or test group died. No differences were noted in gross findings or organ weights between the control and test animals.

In another study by the same investigator, male and female rats (12 each per group) were fed 2%, 5%, 10%, or 25% PEG-20 Laurate for 2 years. The growth of rats given 2% to 10% PEG-20 Laurate did not differ from that of control rats. Male rats given 25% PEG-20 Laurate had significant reductions in growth after weeks 26 and 52. Mortality did not differ from that of controls. Behavior and appearance of rats of the test group were normal.

Hepatic cysts and cecal enlargement were observed at necropsy. Three rats of the high-dose group had slight gastric mucosal hyperplasia. The hepatic cysts were unilocular or multilocular, often multiple, and varied in size. The cysts were observed in five rats given 25%, four rats given 10% (smaller and fewer), and one rat each for the remaining groups. All hepatic cysts but one were in surviving animals. Cecal enlargement occurred in 17 rats fed 25%, 4 rats fed 10%, 3 rats fed 5%, 1 rat fed 2%, and 0 rats fed the control diet, respectively (male plus female rats). The most affected ceca had approximately three times the normal volume, and the enlargement appeared to be both a distention and increase in mass. The common bile duct was not enlarged.

When 61 rats were sectioned microscopically, the hepatic cysts were of bile duct origin, and were lined by columnar epthelium. No generalized intrahepatic bile duct dilatation was observed, but in several instances, the ducts adjacent to the cysts had slight proliferation or dilatation. Hepatic cells were not affected by treatment with PEG-20 Laurate. The ceca of the treated rats did not differ microscopically from the controls, with the exception of distention (evidenced by thinner wall and short glands) in parts of the sections. The stomachs of four rats given 25% and one rat given 10% had slight squamous epithelial hyperplasia, with "low-grade" inflammation within and under the hyperplastic epithelium (at the junction of the two main portions of the stomach). The heart, lungs, spleen, pancreas, small intestine, colon, kidneys, adrenal glands, testes, ovaries, uterus, thyroid gland, parathyroid glands, prostate, urinary bladder, leg bones and muscles, and bone marrow were not affected by treatment with PEG-20 Laurate.

Polyethylene Glycol

Toxic effects were not observed in groups of dogs fed 2% PEG-8, PEG-32, or PEG-75 for 1 year (Andersen 1993).

Skin Irritation

Laureths

Undiluted Laureth-4 produced edema in intact and abraded rabbit skin at 72 hours after 24-hours patch testing. A bath oil product containing 1.8% Laureth-4 (undiluted or in 2% aqueous suspension), applied to the skin of six rabbits per group for 4 hours under occlusion, produced no irritation (Elder 1983b).

PEGs Stearate

Skin irritation was slight when PEG Stearate compounds were tested at 100% concentrations in experimental test animals. PEG-2, -6, -8, -12, -20, -32, -40, and -150 Stearate were nonirritating in primary irritation patch tests using rabbits (Elder 1983a).

Polyethylene Glycol

The PEGs were not irritating to the skin of rabbits or guinea pigs. In irritation tests, undiluted PEG-6 was applied to the skin of rabbits for 4 hours and 50% PEG-75 was applied to the skin of guinea pigs for 4 days and to rabbits over a 13-week period (Andersen 1993).

Lauric Acid

Six rabbits were used in a 24-hour, single-insult occlusive patch test to determine the skin irritancy potential of Lauric Acid. Commercially supplied Lauric Acid and a product formulation containing 8.7% Lauric Acid (as a 5% aqueous solution) were applied to intact and abraded skin sites at a dose volume of 0.5 ml. The primary irritation index (PII; maximum = 8.00) of the commercially supplied Lauric Acid was 1.12; signs of irritation included minimal erythema at 24 hours, and minimal edema at several abraded test sites at 72 hours. Rabbits treated with the product formulation had no signs of irritation (PII = 0) (Elder 1987).

Skin Sensitization

PEGs Stearate

PEG-2 Stearate (as a 0.1% suspension) was evaluated for dermal sensitization potential using guinea pigs and the Landsteiner and Jacobs sensitization procedure. Under the test conditions, PEG-2 Stearate was nonsensitizing. Likewise, PEG-8 and -40 Stearate were nonsensitizers (Elder 1983a).

Polyethylene Glycol

PEG-75 was not a sensitizer. In the guinea pig skin sensitization test, PEG-75 was tested at a concentration of 0.1% (Andersen 1993).

Ocular Irritation

Laureths

Undiluted Laureth-4 was moderately irritating, and 10% and 20% dilutions were minimally irritating to eyes of rabbits. An undiluted body shampoo containing 17% Laureth-4 produced irritation when instilled into the conjunctival sac of rabbits. An undiluted bath oil containing 1.8% Laureth-4 produced only transient mild conjunctivitis, which disappeared by 72 hours (Elder 1983b).

PEGs Laurate

PEG-12 Laurate (pH = 7.6) at a concentration of 1% did not cause ocular irritation in rabbits (Hopper et al. 1949).

PEGs Stearate

PEGs Stearate produced minimal ocular irritation when tested at concentrations up to 100% (Elder 1983a).

Polyethylene Glycol

PEG-6 and -75 did not cause corneal injuries when instilled (undiluted, 0.5 ml) into the conjunctival sac of rabbits. PEG-8 (35% solution, 0.1 ml) and PEG-32 (melted in water bath, 0.1 ml) induced mild ocular irritation in rabbits (Andersen 1993).

Lauric Acid

Lauric Acid (as commercially supplied) caused persistent corneal opacity, mild conjunctivitis, and iritis to the eyes of six albino rabbits. The mean ocular irritation scores were 35 after 24 hours, 39 after 48 hours, and 41 after 72 hours. Ocular irritation was not observed after a product formulation (8.7% Lauric Acid; 8.0% aqueous dilution) was instilled into the conjunctival sacs of six New Zealand white rabbits. A soap formulation containing 1.95% Lauric Acid (1% aqueous dilution) caused maximum mean scores of 0.3 for unrinsed eyes (three per group) and 0.7 for rinsed eyes (six per group). New Zealand white rabbits treated with the soap prior to rinsing had grade 1 conjunctival erythema. Treated, unrinsed eyes had no signs of ocular irritation (Elder 1987).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Ethylene Glycol and Its Ethers

It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers (e.g., methoxyethanol, also known as ethylene glycol monomethyl ether) are reproductive and developmental toxins. The CIR Expert Panel undertook a separate, limited review of these compounds in order to assess the possibility that PEG-derived cosmetic ingredients could present similar concerns (CIR 1996). In summary, this report concluded that the ethylene glycol monoalkyl ethers are not themselves toxic, but rather that one or more alcohol or aldehyde dehydrogenase metabolites are toxic. From the available data, the report also concluded that the toxicity of the monoalkyl ethers is inversely proportional to the length of the alkyl chain (methyl is more toxic than ethyl than propyl than butyl, etc.). In particular, because the PEG Laurate and PEG Dilaurate compounds are diesters of polyethylene glycol, and as such, are chemically different from alkyl ethers, the Panel concluded no reproductive or developmental hazards are expected to be posed by these compounds.

Laureths

No abnormalities were found in teratogenicity, multiple generation, fertility, and peri- and postnatal development studies in rats exposed topically to 0.4 ml/kg/day of a 6% Laureth-4 solution (Elder 1983b).

PEGs Stearate

In multigenerational studies, rats fed diets containing 10% to 20% PEG-8 and -40 Stearate had decreased newborn litter survival time due to maternal neglect. Impairment of lactation efficiency as evidenced by lower weanling weights, greater mortality of nurslings, and decreased reproductive performance in the F3 generation were observed in rats fed diet containing 20% PEG-8 and -40 Stearate. No reproductive effects were noted in rats fed 5% PEGs Stearate (Elder 1983a).

Polyethylene Glycol

No adverse reproductive effects occurred during subchronic (90 days) and chronic (2 years) oral toxicity studies of PEG-6-32 and PEG-75. In the subchronic study, PEG-75 was tested at a dose of 0.23 g/kg/day. In the chronic study, PEG-75 was tested at doses up to 0.062 g/kg/day and, PEG-6-32 at doses up to 1.69 g/kg/day (Andersen 1993).

MUTAGENICITY

PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test; the maximum test concentration in both studies was 1%. In the unscheduled DNA synthesis assay, a statistically significant increase in radioactive thymidine incorporation into rat hepatocyte nuclei was noted only at the highest concentration tested (0.1%). PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay when tested at concentrations up to 150 g/l (Andersen 1993).

Lauric Acid at concentrations of 10 to 200 mg/ml increased the incidence of aneuploidy in the D_6 strain of *Saccharomyces cerevisiae*, but did not increase the frequency of mitotic crossing over events. The inhibitory action of Lauric Acid on the mutagenicity of several compounds has been demonstrated using two bacterial systems (Elder 1987).

CARCINOGENICITY

All of the carcinogenicity data available on the PEGs was specifically on PEG-8, which was used as a solvent control for a number of studies. PEG-8 was not carcinogenic when administered orally to mice (30 weeks of dosing), intraperitoneally to rats (6 months of dosing), subcutaneously (20 weeks of dosing for rats; 1 year of dosing for mice), or when injected into the gastric antrum of guinea pigs over a period of 6 months (Andersen 1993).

Lauric Acid was classified as a noncarcinogen after being administered to female BALB/c and CFW mice via subcutaneous injections during two studies. In one study, 16 mice were given 2 injections/week (25 total) of 1 mg Lauric Acid in 0.1 ml tricaprylin. Of the mice, five were alive at 18 months. The mice

had one subcutaneous sarcoma, one pulmonary tumor, and two leukemia-lymphomas at 4 and 5 months. In the second study, 15 mice were injected with 5.0 mg Lauric Acid in 0.1 ml tricaprylin (3 injections/week; 10 total). Eight mice were alive at 18 months, and they had one pulmonary tumor and one leukemia-lymphoma at 23 months.

Lauric Acid dissolved in chloroform (concentration not given) stimulated the formation of skin papillomas, but not the formation of malignant tumors during tumor promotion studies. Several fats and oils, including Lauric Acid, produced acanthosis of guinea pig skin. Upon continued topical application, the acanthosis gradually receded.

Lauric Acid (8 mg/day; in Polysorbate 80) was an inhibitor of Ehrlich ascites tumor in vivo after the tumor was implanted into Swiss albino mice of strain ddy. The survival time of treated mice versus mice of the control group more than doubled (Elder 1987).

CLINICAL STUDIES

Laureths

Laureth-23 did not produce cutaneous irritation in 50 subjects treated with a 60% solution, although undiluted Laureth-23 did cause erythema in one subject. Repeated Insult Patch Test (RIPT) studies using 96 and 150 subjects found no evidence of sensitization for Laureth-23, nor was there evidence of phototoxicity or photoallergenicity (Elder 1983b).

PEGs Stearate

Clinical studies of the PEGs Stearate indicate that these ingredients are neither irritants nor sensitizers, and no evidence of phototoxicity or photosensitization was observed in studies of the ingredient alone or in formulation. PEG-2 Stearate (25% aqueous) did not induce skin irritation or sensitization in a RIPT involving 168 subjects. Neither photosensitization nor phototoxic reactions to PEG-2 Stearate were noted in a group of 28 subjects. Reactions also were not observed in 10 subjects patch tested (two 48-hour applications) with undiluted PEG-100 Stearate, and the same was true for 188 subjects patch tested (RIPT) with a skin conditioner containing 1% to 3% PEG-100 Stearate. A skin conditioner containing 1% to 3% PEG-100 Stearate also was not phototoxic to human subjects (Elder 1983a).

Polyethylene Glycol

In clinical studies, PEG-6 and PEG-8 induced mild sensitization in 9% and 4% of 23 male subjects tested, respectively. However, later production lots of PEG-6, as well as PEG-75, did not cause reactions in any of the 100 male and 100 female subjects tested. A product formulation containing 3% PEG-8 induced minimal to mild irritation (induction phase) in over 75% of 90 volunteers participating in a skin irritation and sensitization study. Responses (not classified) were noted in 22 subjects at the 24-hour challenge reading. Cases of systemic toxicity and contact dermatitis in burn patents were attributed to PEG-based topical ointments. The ointment that induced systemic toxicity contained 63% PEG-6, 5% PEG-20, and 32% PEG-75 (Andersen 1993).

Lauric Acid

No irritation or sensitization was observed after 46 to 48 subjects were treated with 1% Lauric Acid (1.95% in liquid soap formulation) during a repeated insult patch test (Elder 1987).

SUMMARY

The PEGs Dilaurate, PEGs Laurate, and PEG-2 Laurate SE are PEG diesters or esters of lauric acid that function as surfactants in cosmetic formulations. In 1997, PEG-8 Dilaurate and PEG-12 Dilaurate were used in 40 cosmetic formulations, and PEG-2, -4, -8, -10, -15, and -200 Laurate were used in 20 formulations. The remaining ingredients from this family had no reports of use. In 1984, data submitted to the FDA indicated that the PEGs Dilaurate and PEGs Laurate were used at concentrations up to 25%.

The CIR Expert Panel has previously reviewed the safety in cosmetics of the PEGs Stearate, PEGs Distearate, PEGs, Laureths, and Lauric Acid. Based on the similarity in chemical structures, data from those evaluations have been used as a further basis for the safety assessment of the PEGs Dilaurate and PEGs Laurate in cosmetics.

These polyoxyethylene ester surfactants and emulsifiers are produced by the ethoxylation of fatty acids during uncatalyzed or alkali-catalyzed reactions. PEG-2 Laurate has been produced by the interesterification of coconut oil with diethylene glycol. PEG-n Laurate could contain unspecified amounts of the lauric acid diester of PEG and unreacted PEG. PEG-6 may contain small, unquantified amounts of monomer and dimers, and samples PEG-32 and PEG-75 contained peroxides as a result of autoxidation. In general, ethoxylated surfactants can contain 1,4-dioxane, a by-product of ethoxylation, which is then removed during purification of the finished products. Traces of the reactants, stearic acid, ethylene oxide, and the catalysts used could remain in the finished product.

Data on the absorption, metabolism, distribution, and excretion of the PEGs Dilaurate and PEGs Laurate were not available. PEG-40 Stearate was hydrolyzed in vitro by pancreatic lipase. In metabolism studies with rats, rabbits, dogs, and humans, the lower-molecular-weight PEGs were absorbed by the digestive tract and excreted in the urine and feces. The PEGs were readily absorbed through damaged skin.

Fatty acids such as Lauric Acid are absorbed, digested, and transported in animals and humans. During labeling studies, radioactivity was found in various tissues, blood, and lymph after oral, IV, IP, and intraduodenal administration of labelled fatty acids. The fatty acids can undergo β-oxidation to yield acetyl-CoA. Placental transfer of the fatty acids has been observed. Lauric Acid is transported via the lymph and portal systems; fatty acids are typically transported esterified to glycerol in chylomicrons and very-low-density lipoproteins.

The acute oral LD_{50} of PEG-12 Laurate was >25 g/kg in Harlan mice. In the same study, the IV LD_{50} was 500 mg/kg. During short-term feeding studies using chicks, concentrations of up to 2% PEG-4 or-8 Laurate did not cause adverse effects. Rats fed a diet containing 15.9 g/kg/day of 25% PEG-20 Laurate had diarrhea, inflammation of the anal region, and blood clots in the anorectal region after 59 days of treatment. In a 70-day study, rats given 5% to 25% PEG-20 Laurate had diarhhea and inflammation of the anal region. The ingredient was irritating to the gastrointestinal tract, but not necrotizing, and monocyte/macrophage hyperplasia and splenic giant cells were noted more frequently in rats of the treated group than rats of the control group. In a chronic oral toxicity study, nine rats were fed 6% PEG-8 Dilaurate for 505 days. Four of the rats in each of the treatment and control groups died. Of the rats given PEG-8 Dilaurate, one had cystic spots on the liver, one had hemorrhagic lungs, and one had a large fibrosarcoma. In microscopic examinations, three rats had focal parenchymal hepatitis. Of the rats of the control group, four had hemorrhagic and congested lungs, one had hypertrophied testes, one had a concretion in the urinary bladder, two had cystic kidneys, and two had hepatic parasites. In microscopic examinations, one control rat had adrenal cortical hyperplasia, two had chronic interstitial nephritis of the kidneys, two had splenic lymphoid hyperplasia, one had focal parenchymal hepatitis, and one had hepatic vacuolization. During another feeding study, rats fed up to 25% PEG-20 Laurate for 2 years had hepatic cysts, cecal enlargement, slight gastric mucosal hyperplasia, and slight squamous epithelial hyperplasia. PEG-12 Laurate at a concentration of 1% did not cause ocular irritation in rabbits.

The IV LD_{50} values in Harlan mice for PEG-8 and -20 Distearate were 365 mg/kg and 220 mg/kg, respectively. The oral LD_{50} values of PEG-2-150 Stearate ranged from >10 g/kg to 32 g/kg in rats. The IP LD_{50} of PEG-8 Stearate in rats was >9 ml/kg. No signs of toxicity were observed when rats were given IP injections of 2.5 g/kg PEG-50 or -100 Stearate. A hair cream containing 1.5% PEG-6 Stearate had an oral LD_{50} of >34.6 g/kg. The acute dermal LD_{50} of 15% PEG-8 Stearate in rabbits was >10 ml/kg; the only effect noted was erythema at the application site at 24 hours. The PEGs Stearate caused only slight skin irritation and minimal ocular irritation when tested at concentrations of 100% in animals. PEG-8, -40, and -100 Stearate did not cause significant changes in growth mortality rates, microscopic observations, or hematological values during long-term feeding studies. In clinical studies, the PEGs Stearate were not irritating or sensitizing when tested at concentrations of 25%. In addition, they did not cause photosensitization. PEG-8 and -40 Stearate did not cause reproductive or developmental effects, and were noncarcinogenic.

In acute toxicity studies, the PEGs had low oral and dermal toxicity. The PEGs were not irritating to the skin of rabbits or guinea pigs, and minimally irritating to the skin of humans. They did not cause sensitization in animal or human studies using intact skin, but sensitization and nephrotoxicity were observed in burn patients that were treated with a PEG-based cream. PEG was determined to be the causative agent in both animal and human studies. In ocular irritation studies, the PEGs caused mild, transient ocular irritation in rabbits. Cosmetic product formulations containing up to 13% Lauric Acid did not cause primary or cumulative irritation and did not cause sensitization. The available data indicated that the PEGs were not mutagenic or carcinogenic.

A product formulation containing 5% Lauric Acid was nontoxic to rats during an oral toxicity study. Transient signs of toxicity (mucoid diarrhea, depression, unkempt fur, etc.) were observed when male rats were fed 0.46 to 10 g/kg Lauric Acid. In this study, one rat died; it had congested lungs and kidneys, and advanced autolytic changes. In a subchronic oral toxicity study, rats fed 10% Lauric Acid had no signs of toxicity. Lauric Acid was also noncarcinogenic in animal tests.

It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers are reproductive and developmental toxins. The PEGs Dilaurate and PEGs Laurate are diesters and esters of PEG and, as such, are chemically different from PEG alkyl ethers. Hence, they are not expected to cause adverse reproductive or developmental effects.

DISCUSSION

The CIR Expert Panel was concerned about the sensitization and toxicity potential of the PEGs Dilaurate and PEGs Laurate when applied to damaged skin. This concern arose because of positive patch tests and incidences of nephrotoxicity in burn patients treated with an antimicrobial cream that contained PEG-6, PEG-20, and PEG-75. PEG was the causative agent in both animal and human studies; no evidence of systemic toxicity or sensitization was found in studies with intact skin.

Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to remove these impurities from the PEG Dilaurate and PEG Laurate ingredients before blending them into cosmetic formulations.

Although few data were available on the PEGs Dilaurate and PEGs Laurate, the Expert Panel concluded that the data on the structurally related ingredients (PEGs Distearate, PEGs Stearate, PEGs, and Lauric Acid) were sufficient. Although current concentration of use data were not available, the highest reported concentration of use in 1984 was 25%. The PEGs Dilaurate and PEGs Laurate were considered safe for use at concentrations up to 25% based upon the results of short-term and chronic oral toxicity studies.

CONCLUSION

On the basis of the available data, the CIR Expert Panel concludes that PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE are safe for use in cosmetics at concentrations up to 25%.

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

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 27, 2014

SUBJECT: Updated Concentration of Use by FDA Product Category: PEG Di-fatty acids

Concentration of Use by FDA Product Category*

PEG-3 Distearate
PEG-4 Distearate
PEG-6 Distearate
PEG-8 Distearate
PEG-9 Distearate
PEG-12 Distearate
PEG-20 Distearate
PEG-32 Distearate
PEG-50 Distearate
PEG-75 Distearate
PEG-120 Distearate
PEG-150 Distearate
PEG-175 Distearate
PEG-2 Distearate
PEG-40 Distearate
PEG-190 Distearate
PEG-250 Distearate
PEG-150 Dibehenate
PEG-3 Dicaprylate/Caprate
PEG-4 Dicocoate
PEG-8 Dicocoate
PEG-4 Diheptanoate
PEG-2 Diisononanoate
PEG-2 Diisostearate
PEG-3 Diisostearate
PEG-4 Diisostearate
PEG-6 Diisostearate
PEG-8 Diisostearate
PEG-12 Diisostearate
PEG-90 Diisostearate
PEG-175 Diisostearate
PEG-2 Dilaurate
PEG-4 Dilaurate
PEG-6 Dilaurate
PEG-8 Dilaurate
PEG-12 Dilaurate
PEG-16 Dilaurate
PEG-20 Dilaurate
PEG-32 Dilaurate
PEG-75 Dilaurate
PEG-150 Dilaurate
PEG-2 Dioleate
PEG-3 Dioleate
PEG-4 Dioleate
PEG-6 Dioleate
PEG-8 Dioleate
PEG-10 Dioleate
PEG-12 Dioleate
PEG-20 Dioleate
PEG-32 Dioleate
PEG-75 Dioleate
PEG-150 Dioleate
PEG-3 Dipalmitate
PEG-8 Ditallate
PEG-12 Ditallate

Ingredient	Product Category	Maximum Concentration of Use
PEG-3 Distearate	Other bath preparations	1.7%
PEG-3 Distearate	Shampoos (noncoloring)	1-3.4%
PEG-3 Distearate	Other hair preparations (noncoloring)	1%
PEG-3 Distearate	Hair rinses (coloring)	2.8%
PEG-3 Distearate	Hair shampoos (coloring)	2.8%
PEG-3 Distearate	Bath soaps and detergents	0.45-1.1%
PEG-3 Distearate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.5-3%
PEG-3 Distearate	Body and hand products not spray	0.45-1.5%
PEG-6 Distearate	Rinses (noncoloring)	1%
PEG-6 Distearate	Other makeup preparations	0.5%
PEG-6 Distearate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.91%
PEG-6 Distearate	Face and neck products not spray	1%
PEG-8 Distearate	Eye liner	0.0091%
PEG-8 Distearate	Eye shadow	0.019-1.2%
PEG-8 Distearate	Eye lotion	0.5%
PEG-8 Distearate	Tonics, dressings and other hair grooming aids	0.3%
PEG-8 Distearate	Deodorants not spray	1-6.5%

PEG-8 Distearate	Aftershave lotions	0.03%
PEG-8 Distearate	Shaving cream	7%
PEG-8 Distearate	Face and neck products not spray	0.5%
PEG-12 Distearate	Hair conditioners	1.5-1.7%
PEG-12 Distearate	Shampoos (noncoloring)	0.2%
PEG-150 Distearate	Baby shampoo	0.75-4.5%
PEG-150 Distearate	Baby lotions, oils and creams not spray	9%
PEG-150 Distearate	Other baby products	2.5-9.4% (rinse-off)
PEG-150 Distearate	Bubble bath	1.5%
PEG-150 Distearate	Other bath preparations	1%
PEG-150 Distearate	Eye shadow	1.7%
PEG-150 Distearate	Eye lotion	0.07-1.8%
PEG-150 Distearate	Hair conditioner	0.21-3%
PEG-150 Distearate	Shampoos (noncoloring)	0.6-4%
PEG-150 Distearate	Tonics, dressings and other hair grooming aids	0.06-2.4%
PEG-150 Distearate	Hair dyes and colors	0.0075-0.15%
PEG-150 Distearate	Blushers	1%
PEG-150 Distearate	Foundations	1%
PEG-150 Distearate	Lipstick	0.05%
PEG-150 Distearate	Bath soaps and detergents	0.0003-4.5%
PEG-150 Distearate	Douches	0.9%
PEG-150 Distearate	Aftershave lotion	0.03%
PEG-150 Distearate	Preshave lotions	1%
PEG-150 Distearate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.4-33.2%
PEG-150 Distearate	Face and neck products not spray	0.25-0.6%
PEG-150 Distearate	Body and hand products not spray	0.024-2.5%
PEG-150 Distearate	Moisturizing products not spray	0.028-1.5%
PEG-150 Distearate	Night products not spray	0.025-0.35%
PEG-150 Distearate	Paste masks and mud packs	0.4%
PEG-150 Distearate	Indoor tanning preparations	0.15%
PEG-175 Distearate	Shaving cream	0.089%
PEG-2 Distearate	Foundations	0.001%
PEG-2 Distearate	Aftershave lotion	0.001%
PEG-8 Dicocoate	Hair conditioners	0.04%
PEG-8 Dicocoate	Tonics, dressings and other hair grooming aids	0.04%
PEG-8 Dicocoate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.04-0.08%
PEG-4 Diheptanoate	Eye shadow	0.04-8%
PEG-4 Diheptanoate	Eye lotion	1%

PEG-4 Diheptanoate	Foundation	6.9%
PEG-4 Diheptanoate	Lipstick	0.07-14%
PEG-4 Diheptanoate	Other makeup preparations	0.02%
PEG-4 Diheptanoate	Body and hand products not spray	14.3%
PEG-4 Diheptanoate	Night products not spray	1.5%
PEG-2 Diisononanoate	Nail creams and lotions	1.7%
PEG-8 Diisostearate	Eye makeup remover	4.5%
PEG-8 Diisostearate	Deodorant not spray	2%
PEG-8 Diisostearate	Skin cleansing (cold creams, cleansing lotions, liquid and pads)	1.5-4.5%
PEG-8 Diisostearate	Face and neck products not spray	0.5%
PEG-8 Diisostearate	Moisturizing products not spray	0.5%
PEG-12 Diisostearate	Eye makeup remover	2.3%
PEG-12 Diisostearate	Tonics, dressings and other hair grooming aids not spray	4%
PEG-12 Diisostearate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	2.3-10%
PEG-90 Diisostearate	Deodorant not spray	2.1%
PEG-90 Diisostearate	Shaving cream	0.029%
PEG-175 Diisostearate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	5%
PEG-4 Dilaurate	Eye lotion	0.04-2%
PEG-4 Dilaurate	Eye makeup remover	0.27%
PEG-4 Dilaurate	Hair conditioner	0.06%
PEG-4 Dilaurate	Shampoos (noncoloring)	0.036-072%
PEG-4 Dilaurate	Tonics, dressings and other hair grooming aids	0.036%
PEG-4 Dilaurate	Foundation	0.032-0.04%
PEG-4 Dilaurate	Aftershave lotion	0.04%
PEG-4 Dilaurate	Preshave lotion	0.036%
PEG-4 Dilaurate	Other shaving preparations	0.028%
PEG-4 Dilaurate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.036-0.51%
PEG-4 Dilaurate	Face and neck products not spray	0.036-0.25%
PEG-4 Dilaurate	Moisturizing products not spray	0.04-0.08%
PEG-4 Dilaurate	Night products not spray	0.036%
PEG-4 Dilaurate	Suntan products not spray	12%

	pump spray	0.072%
PEG-8 Dilaurate	Bath oils, tablets and salts	0.05-5%
PEG-8 Dilaurate	Other bath preparations	15%
PEG-8 Dilaurate	Eye makeup removers	0.18%
PEG-8 Dilaurate	Hair conditioners	6%
PEG-8 Dilaurate	Tonics, dressings and other hair grooming aids	6%
PEG-8 Dilaurate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.23-1%
PEG-8 Dioleate	Mascara	1%
PEG-8 Dioleate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	5%
PEG-12 Dioloeate	Hair conditioners	0.12%
PEG-12 Dioloeate	Hair sprays pump spray	 0.024%
PEG-12 Dioloeate	Tonics, dressings and other hair grooming aids	0.024%
PEG-12 Dioloeate	Makeup bases	0.1%
PEG-12 Dioloeate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1%
PEG-12 Dioloeate	Face and neck products not spray	 0.15%
PEG-12 Dioloeate	Body and hand products not spray	 0.14%
PEG-12 Dioloeate	Moisturizing products not spray	 0.12%
PEG-12 Dioloeate	Suntan products not spray	 4.5%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2014

Table prepared July 30, 2014

Updated October 27, 2014: PEG-150 Distearate: baby shampoo high concentration increased from 3% to 4.5%; added baby lotions, oils and creams; other baby products added 9.4% high concentration; hair conditioners high concentration increased from 0.3% to 3%; added douches; skin cleansing high concentration increased from 3.5% to 33.2%; moisturizing products high concentration increased from 0.35% to 1.5%; PEG-8 Diisostearate: skin cleansing low concentration decreased from 4% to 1.5%; PEG-4 Dilaurate: tonics, dressings and other hair grooming aids added high concentration 0.072%; added other shaving preparations; moisturizing products added high concentration 0.08%; added suntan products

2014 VCRP Data for PEG Diesters

05A - Hair Conditioner	PEG-12 DISTEARATE	2
05E - Rinses (non-coloring)	PEG-12 DISTEARATE	4
07C - Foundations	PEG-12 DISTEARATE	1
		7

10A - Bath Soaps and Detergents	PEG-120 DISTEARATE	6
10E - Other Personal Cleanliness Products	PEG-120 DISTEARATE	1
		7

01A - Baby Shampoos	PEG-150 DISTEARATE	15
01C - Other Baby Products	PEG-150 DISTEARATE	10
02A - Bath Oils, Tablets, and Salts	PEG-150 DISTEARATE	1
02B - Bubble Baths	PEG-150 DISTEARATE	23
02D - Other Bath Preparations	PEG-150 DISTEARATE	10
03C - Eye Shadow	PEG-150 DISTEARATE	2
03D - Eye Lotion	PEG-150 DISTEARATE	2
03G - Other Eye Makeup Preparations	PEG-150 DISTEARATE	2
05A - Hair Conditioner	PEG-150 DISTEARATE	67
05E - Rinses (non-coloring)	PEG-150 DISTEARATE	1
05F - Shampoos (non-coloring)	PEG-150 DISTEARATE	101
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-150 DISTEARATE	4
05I - Other Hair Preparations	PEG-150 DISTEARATE	1
07A - Blushers (all types)	PEG-150 DISTEARATE	2
07B - Face Powders	PEG-150 DISTEARATE	1
07I - Other Makeup Preparations	PEG-150 DISTEARATE	1
10A - Bath Soaps and Detergents	PEG-150 DISTEARATE	150
10B - Deodorants (underarm)	PEG-150 DISTEARATE	1
10C - Douches	PEG-150 DISTEARATE	1
10E - Other Personal Cleanliness Products	PEG-150 DISTEARATE	190
11A - Aftershave Lotion	PEG-150 DISTEARATE	1
11E - Shaving Cream	PEG-150 DISTEARATE	1
12A - Cleansing	PEG-150 DISTEARATE	38
12C - Face and Neck (exc shave)	PEG-150 DISTEARATE	8
12D - Body and Hand (exc shave)	PEG-150 DISTEARATE	4
12F – Moisturizing	PEG-150 DISTEARATE	7
12G – Night	PEG-150 DISTEARATE	1
12H - Paste Masks (mud packs)	PEG-150 DISTEARATE	5

12J - Other Skin Care Preps	PEG-150 DISTEARATE	3
13B - Indoor Tanning Preparations	PEG-150 DISTEARATE	1
		654

11A - Aftershave Lotion	PEG-2 DISTEARATE	2
12C - Face and Neck (exc shave)	PEG-2 DISTEARATE	2
12F - Moisturizing	PEG-2 DISTEARATE	1
12G - Night	PEG-2 DISTEARATE	1
		6

02B - Bubble Baths	PEG-250 DISTEARATE	2
02D - Other Bath Preparations	PEG-250 DISTEARATE	3
10A - Bath Soaps and Detergents	PEG-250 DISTEARATE	12
10E - Other Personal Cleanliness Products	PEG-250 DISTEARATE	4
		21

05F - Shampoos (non-coloring)	PEG-3 DISTEARATE	15
10A - Bath Soaps and Detergents	PEG-3 DISTEARATE	10
10E - Other Personal Cleanliness Products	PEG-3 DISTEARATE	3
12A - Cleansing	PEG-3 DISTEARATE	22
		50

05A - Hair Conditioner	PEG-4 DISTEARATE	1

12A - Cleansing	PEG-50 DISTEARATE	1

11E - Shaving Cream	PEG-6 DISTEARATE	1

03C - Eye Shadow	PEG-8 DISTEARATE	1
03G - Other Eye Makeup Preparations	PEG-8 DISTEARATE	1
05A - Hair Conditioner	PEG-8 DISTEARATE	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-8 DISTEARATE	3
10B - Deodorants (underarm)	PEG-8 DISTEARATE	10
10E - Other Personal Cleanliness Products	PEG-8 DISTEARATE	4
11A - Aftershave Lotion	PEG-8 DISTEARATE	15
11D - Preshave Lotions (all types)	PEG-8 DISTEARATE	1
11G - Other Shaving Preparation Products	PEG-8 DISTEARATE	3
12A - Cleansing	PEG-8 DISTEARATE	1
12D - Body and Hand (exc shave)	PEG-8 DISTEARATE	3
12F - Moisturizing	PEG-8 DISTEARATE	2
12J - Other Skin Care Preps	PEG-8 DISTEARATE	2
		48

03C - Eye Shadow	PEG-4 DIHEPTANOATE	3
03D - Eye Lotion	PEG-4 DIHEPTANOATE	1
03G - Other Eye Makeup Preparations	PEG-4 DIHEPTANOATE	1
07E - Lipstick	PEG-4 DIHEPTANOATE	9
07G - Rouges	PEG-4 DIHEPTANOATE	1
12D - Body and Hand (exc shave)	PEG-4 DIHEPTANOATE	2
12F - Moisturizing	PEG-4 DIHEPTANOATE	1
12G - Night	PEG-4 DIHEPTANOATE	1
		19

03E - Eye Makeup Remover	PEG-12 DIISOSTEARATE	1
12A - Cleansing	PEG-12 DIISOSTEARATE	4
		5

12J - Other Skin Care Preps	PEG-175 DIISOSTEARATE	1

10E - Other Personal Cleanliness Products	PEG-6 DIISOSTEARATE	1

03E - Eye Makeup Remover	PEG-8 DIISOSTEARATE	1
07I - Other Makeup Preparations	PEG-8 DIISOSTEARATE	1
12A - Cleansing	PEG-8 DIISOSTEARATE	7
12C - Face and Neck (exc shave)	PEG-8 DIISOSTEARATE	1
12D - Body and Hand (exc shave)	PEG-8 DIISOSTEARATE	2
		12

02B - Bubble Baths	PEG-90 DIISOSTEARATE	1
10A - Bath Soaps and Detergents	PEG-90 DIISOSTEARATE	8
10B - Deodorants (underarm)	PEG-90 DIISOSTEARATE	2
		11

02A - Bath Oils, Tablets, and Salts	PEG-4 DILAURATE	5
03D - Eye Lotion	PEG-4 DILAURATE	2
03E - Eye Makeup Remover	PEG-4 DILAURATE	5
03G - Other Eye Makeup Preparations	PEG-4 DILAURATE	1
05A - Hair Conditioner	PEG-4 DILAURATE	5
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-4 DILAURATE	1
07C - Foundations	PEG-4 DILAURATE	1
07I - Other Makeup Preparations	PEG-4 DILAURATE	1
10E - Other Personal Cleanliness Products	PEG-4 DILAURATE	2
11A - Aftershave Lotion	PEG-4 DILAURATE	3
12A - Cleansing	PEG-4 DILAURATE	2
12C - Face and Neck (exc shave)	PEG-4 DILAURATE	3
12F - Moisturizing	PEG-4 DILAURATE	5
12J - Other Skin Care Preps	PEG-4 DILAURATE	1
		37

02A - Bath Oils, Tablets, and Salts	PEG-8 DILAURATE	6
03E - Eye Makeup Remover	PEG-8 DILAURATE	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-8 DILAURATE	5
12A - Cleansing	PEG-8 DILAURATE	1
		14

10A - Bath Soaps and Detergents	PEG-12 DIOLEATE	1
12A - Cleansing	PEG-12 DIOLEATE	1
		2

02A - Bath Oils, Tablets, and Salts	PEG-8 DIOLEATE	2
03F - Mascara	PEG-8 DIOLEATE	2
		4