Safety Assessment of PEGs Cocamine and Related Ingredients as Used in Cosmetics

Status:	Draft Final Amended Report
Release Date:	May 22, 2015
Panel Date:	June 15-16, 2015

The 2015 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 Ivan J. Boyer, Ph.D., Senior Toxicologist, Christina L. Burnett, Senior Scientific Analyst/Writer, and Bart Heldreth, Ph.D., Chemist.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer, PhD, DABT
Senior Toxicologist
Date: May 22, 2015
Subject: Draft Final Amended Safety Assessment of PEGs Cocamine and Related Ingredients

Enclosed is the draft final amended safety assessment for PEGs cocamine and related ingredients (*pgcoca062015_FR* in the pdf document).

The final amended safety assessment report is accompanied by the following attachment:

- Transcripts of the March 2015 and December 2014 CIR Expert Panel meetings (*pgcoca062015_tmin*)

The transcripts of the relevant Panel meetings of 2011 and 2012 and the original (1999) safety PEGs cocamine safety assessment report were included in the "admin book" of the December 2014, which is available by CTRL-clicking http://www.cir-safety.org/sites/default/files/admin_web.pdf. The minutes are on pdf pages 164 to 193, and the original report is on pdf pages 342 to 349.

In addition, the Personal Care Products Council (PCPC) submitted comments on the draft safety assessment report a few days before the March 2015 meeting and on the tentative amended safety assessment report since the March 2015, including:

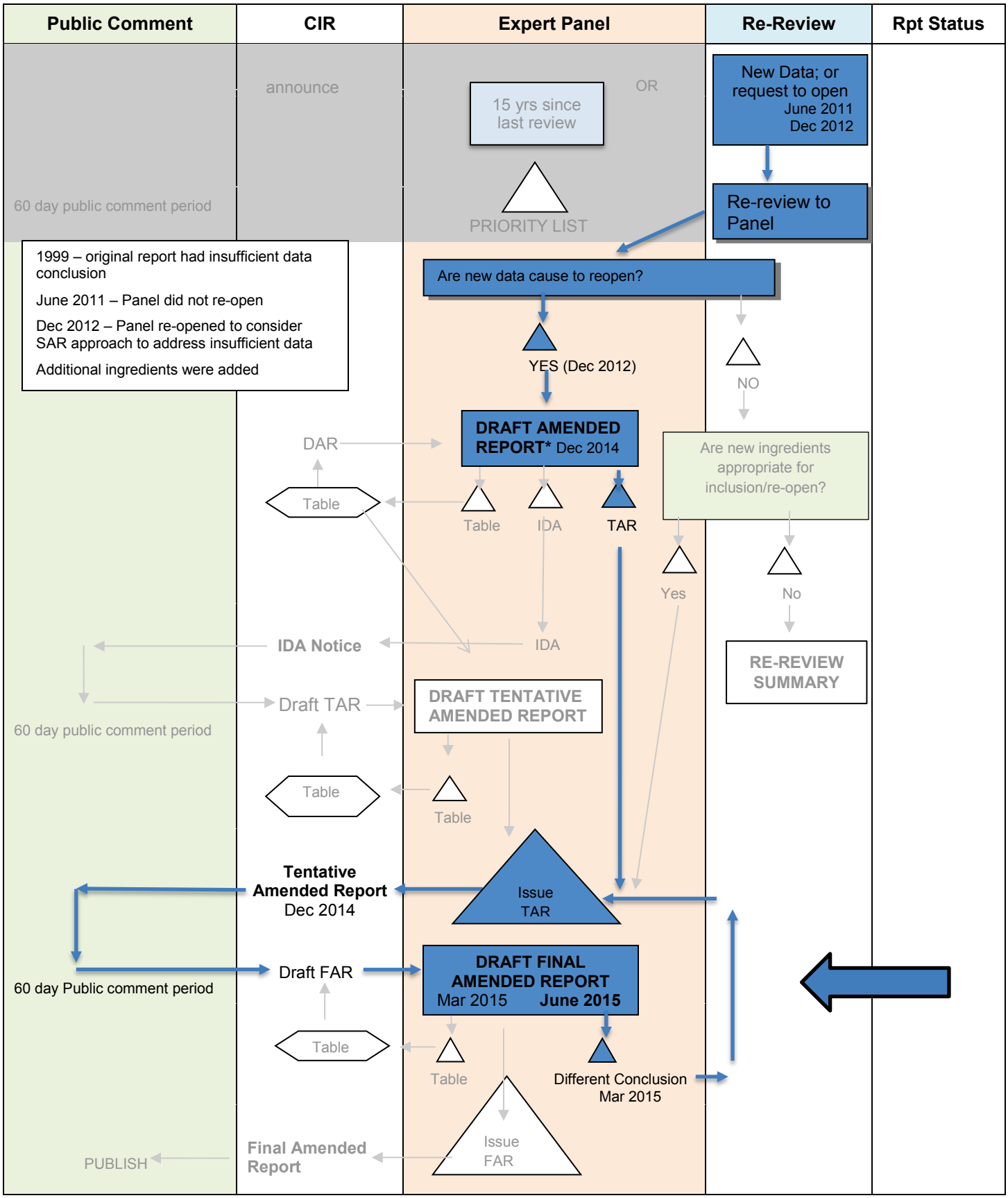
- Comments on the Draft Report Prepared for the March 16-17,2015 CIR Expert Panel Meeting: Safety Assessment of PEGs Cocamine and Related Ingredients as Used in Cosmetics (*pgcoca062015_PCPC1*)

- Comments on the Tentative Amended Report: Safety Assessment of PEGs Cocamine and Related ingredients as Used in Cosmetics (*pgcoca062015_PCPC2*)

Further, the PCPC submitted Summaries of Sensitization Studies PEG-2 Tallow Amine (*pgcoca062015_data1*), dated April 21, 2015, which replaces Summaries of Sensitization Studies PEG-2 Hydrogenated Tallow Amine, dated January 14, 2015. The new submission corrects the previous submission, which incorrectly identified PEG-2 hydrogenated tallow amine (rather than PEG-2 tallow amine) as the compound tested in the sensitization studies summarized. The final amended safety assessment report reflects that change.

Also, please note that a dermal sensitization test of PEG-2 oleamine was found in the European Chemicals Agency (ECHA) online database, and a summary of that test has been incorporated into the final amended safety assessment report.

After reviewing the information provided in the present safety assessment report and accompanying material, the Panel should determine whether the data are sufficient to affirm the Panel's conclusion as stated at the March 2015 meeting, and if so, issue a Final Amended Report



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

History of Panel Actions for PEGs cocamine:

March 16-17, 1995

Insufficient Data Announcement issued for the following data needs:

(1) Concentration of use

(2) Physical and chemical properties (including impurities and stability)

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

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

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

(6) Ocular irritation, if available

(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 22-23, 1995

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

(1) Concentrations of use

(2) Physical and chemical properties (including impurities and stability)

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

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

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

(6) Ocular irritation, if available

(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.

March 4-5, 1996

Tentative Final Report with insufficient data conclusion issued for public comment. The data that are needed in order for the Panel to complete its safety assessment of these ingredients are listed in the discussion section of the report as follows:

(1) Purity of the actual product, particularly in light of any contaminants

(2) Physical properties, particularly the lipid partition coefficient

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

September 19-20, 1996

The Panel voted unanimously in favor of issuing a Final Report with an insufficient data conclusion. The data that are needed for completion of this safety assessment are listed in the report discussion as follows:

(1) Physical properties and chemical impurities, especially nitrosamines

(2) Genotoxicity in a mammalian system; if the results are positive, then a dermal carcinogenesis study using NTP methods may be needed

(3) 28-day dermal toxicity study using PEG-2 cocamine

(4) Dermal sensitization data on PEG-2 cocamine

June 27-28, 2011

The Panel voted unanimously against re-opening PEGs cocamine

The Personal Care Products Council's CIR Science and Support Committee submitted data and structure/activity analyses for these PEGs cocamine ingredients. The Expert Panel determined that the structure/activity analysis approaches were not well enough established to substitute for actual study data that had been requested. The Panel recognized the potential of such analyses and recommended that a part of an upcoming meeting agenda (on the order of ½ day) be devoted to discussing how such approaches might be used by CIR in the future.

March 5-6, 2012

In June of 2011, the CIR Expert Panel had asked for a workshop that would address the use of structure activity relationships (SAR) in toxicological evaluations. Four speakers, representing diverse areas of responsibility, each addressed the current status of the use of SAR.

December 10-11, 2012

The Panel voted unanimously to re-open PEGs cocamine. The Panel reviewed newly provided data and determined to reopen the safety assessment of PEGs cocamine published in 1999, and add 41 related ingredients, bringing the total number of ingredients in the report to 47.

December 8-9, 2014

The Panel reviewed a strategy memorandum for the 47 PEGs cocamine and related ingredients, and decided to issue a tentative amended safety assessment with the conclusion that 32 ingredients in this group are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating. However, the Expert Panel requested additional data to support the safety of the smaller PEGs cocamine and related ingredients.

The additional data needed for these ingredients were

(1) physical and chemical properties, including impurities (especially nitrosamines)
(2) genotoxicity in a mammalian test system (if the results are positive then a dermal carcinogenesis study may be needed)
(3) 28-day dermal toxicity using PEG-2 cocamine
(4) dermal sensitization data on PEG-2 cocamine

The Panel also noted the absence of use concentration data for PEG-2 rapeseedamine, in particular, because this ingredient had the greatest use frequency (255) reported to the VCRP.

March 16-17, 2015

The Panel reviewed a draft final amended safety assessment report for the 47 PEGs cocamine and related ingredients, and decided to issue a tentative final amended safety assessment with the conclusion that all 47 PEGs cocamine and related ingredients are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating.

The Panel noted that the tallow moieties of several of the selected analogs, including PEG-2 tallow amine, have greater susceptibility to epoxidation and hydroperoxidation than the fatty acid moieties of the PEGs cocamine and other related ingredients. Thus, the incorporation of toxicity data available for these analogs represents a conservative approach to the read-across analysis of the entire ingredient group. The equivocal results of a local lymph node assay (LLNA) of PEG-2 hydrogenated tallow amine were confounded by the irritant properties of the ingredient, and were not consistent with the negative results of a guinea pig maximization test. The Panel noted that exposure durations and frequencies for the smaller ingredients in this group would be relatively low, because these ingredients are used predominantly in rinse-off hair-coloring products.

PEGs Cocamine Ingredients Data Profile – March 2015 – Writers, Ivan Boyer, Christina Burnett and Bart Heldreth															
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Tocikokinetics	Acute Toxicity	Repeated Dose Toxicity	Repro. /Develop. Toxicity	Genotoxicity	Carcinogenicity	Irritation/Sensitization - Animal	Irritation/Sensitization - Clinical	Ocular/Mucosal	Phototoxicity	Case Studies
Ingredients															
PEG-2 cocamine[a,b]	X	X	X	X		X	(X)[c]	(X)[c]			X[d]		X		
PEG-3 cocamine	X		X	X											
PEG-4 cocamine[a,b]			X	X	M				M		M				
PEG-5 cocamine	X	X	X	X			X						X		
PEG-8 cocamine			X	X											
PEG-10 cocamine[a,b]			X	X											
PEG-12 cocamine			X	X											
PEG-15 cocamine[a,b]	X	X	X	X			X		X		X[d]	X	X	X	
PEG-20 cocamine			X	X											
PEG-2 hydrogenated tallow amine		X	X								X				
PEG-5 hydrogenated tallow amine	X	X	X												
PEG-8 hydrogenated tallow amine	X		X												
PEG-10 hydrogenated tallow amine			X												
PEG-15 hydrogenated tallow amine			X												
PEG-20 hydrogenated tallow amine			X												
PEG-30 hydrogenated tallow amine			X												
PEG-40 hydrogenated tallow amine			X												

PEGs Cocamine Ingredients Data Profile – March 2015 – Writers, Ivan Boyer, Christina Burnett and Bart Heldreth															
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Tocikokinetics	Acute Toxicity	Repeated Dose Toxicity	Repro. /Develop. Toxicity	Genotoxicity	Carcinogenicity	Irritation/Sensitization - Animal	Irritation/Sensitization - Clinical	Ocular/Mucosal	Phototoxicity	Case Studies
PEG-50 hydrogenated tallow amine			X												
PEG-2 lauramine			X												
PEG-2 oleamine	X		X									X			
PEG-5 oleamine		X	X												
PEG-6 oleamine			X												
PEG-10 oleamine			X												
PEG-15 oleamine		X	X												
PEG-20 oleamine			X												
PEG-25 oleamine			X												
PEG-30 oleamine			X												
PEG-12 palmitamine			X	X											
PEG-2 rapseedamine	X		X	X											
PEG-2 soyamine	X		X	X											
PEG-5 soyamine	X	X	X	X											
PEG-8 soyamine			X	X											
PEG-10 soyamine			X	X											
PEG-15 soyamine		X	X	X											
PEG-2 stearamine			X												
PEG-5 stearamine		X	X												
PEG-10 stearamine		X	X												
PEG-15 stearamine		X	X												
PEG-50 stearamine			X												
PEG-2 tallow amine	X	X	X	X											
PEG-7 tallow amine			X	X											
PEG-11 tallow amine			X	X											

PEGs Cocamine Ingredients Data Profile – March 2015 – Writers, Ivan Boyer, Christina Burnett and Bart Heldreth															
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Tocikokinetics	Acute Toxicity	Repeated Dose Toxicity	Repro. /Develop. Toxicity	Genotoxicity	Carcinogenicity	Irritation/Sensitization - Animal	Irritation/Sensitization - Clinical	Ocular/Mucosal	Phototoxicity	Case Studies
PEG-15 tallow amine[b]		X	X	X			X	X	X						
PEG-20 tallow amine[b]			X	X			X		X		X				
PEG-22 tallow amine			X	X											
PEG-25 tallow amine			X	X											
PEG-30 tallow amine			X	X											
Additional Substances (Analogs)															
Ethoxylated C13-15 alkylamines[b]			X				X								
PEG-8 stearamine[b]			X						X						
POE-5/POP-12 tallow amine[b]							X								
Tallow bis(2-hydroxyethyl) amine[b]			X				X		X		X				

"X" indicates that data were available in the category for that ingredient.
"M" indicates computational modelling
Shaded cells indicate ingredients that have been previously reviewed by CIR.
[a]Selected as a structure of interest (SOI)
[b]Identified as an analog
[c]Search for evidence of systemic toxicity and developmental and reproductive toxicity (DART) in a DART screening study
[d]Test(s) included search for evidence of irritation, but not sensitization

Search Strategy for PEGs Cocamine and Related Ingredients

- PubMed – September 19, 2014
    - Search for "PEG Cocamine" OR "PEG-2 Cocamine" OR "PEG-3 Cocamine" OR "PEG-5 Cocamine" OR "PEG-10 Cocamine" OR "PEG-15 Cocamine" OR "PEG-20 Cocamine" OR "PEG-4 Cocamine" OR "PEG-8 Cocamine" OR "PEG-12 Cocamine" OR "PEG Hydrogenated Tallow Amine" OR "PEG-2 Hydrogenated Tallow Amine" OR "PEG-5 Hydrogenated Tallow Amine" OR "PEG-8 Hydrogenated Tallow Amine" OR "PEG-10 Hydrogenated Tallow Amine" OR "PEG-15 Hydrogenated Tallow Amine" OR "PEG-20 Hydrogenated Tallow Amine" OR "PEG-30 Hydrogenated Tallow Amine" OR "PEG-40 Hydrogenated Tallow Amine" OR "PEG-50 Hydrogenated Tallow Amine" OR "PEG-2 Lauramine" OR "PEG Oleamine" OR "PEG-2 Oleamine" OR "PEG-5 Oleamine" OR "PEG-6 Oleamine" OR "PEG-10 Oleamine" OR "PEG-15 Oleamine" OR "PEG-20 Oleamine" OR "PEG-25 Oleamine" OR "PEG-30 Oleamine" OR "PEG-12 Palmitamine" OR "PEG-2 Rapseedamine" OR "PEG Soyamine" OR "PEG-2 Soyamine" OR "PEG-5 Soyamine" OR "PEG-8 Soyamine" OR "PEG-10 Soyamine" OR "PEG-15 Soyamine" OR "PEG Stearamine" OR "PEG-2 Stearamine" OR "PEG-5 Stearamine" OR "PEG-10 Stearamine" OR "PEG-15 Stearamine" OR "PEG-50 Stearamine" OR "PEG Tallow Amine" OR "PEG-2 Tallow Amine" OR "PEG-7 Tallow Amine" OR "PEG-11 Tallow Amine" OR "PEG-15 Tallow Amine" OR "PEG-20 Tallow Amine" OR "PEG-22 Tallow Amine" OR "PEG-25 Tallow Amine" OR "PEG-30 Tallow Amine" OR "2,2'-(Octadecylimino)Bisethanol" OR "bis(2-Hydroxyethyl)dodecylamine" OR "Ethanol, 2,2'-(Dodecylimino)bis-" OR "Ethanol, 2,2'-(Octadecylimino)Bis-" OR "Ethanol, 2,2'-iminobis-, N-coco alkyl derivatives" OR "N,N-bis(2-Hydroxyethyl)lauramine" OR "N,N-Bis(2-Hydroxyethyl)-N-Octadecylamine" OR "N-Lauryl Diethanolamine" OR "N-Stearyldiethanolamine" OR "PEG-15 Tallow Amine" OR "PEG-2 Tallow Amine" OR "PEG-20 Tallow Amine" OR "PEG-30 Tallow Amine" OR "PEG-40 Tallow Amine" OR "PEG-5 Tallow Amine" OR "PEG-50 Tallow Amine" OR "PEG-8 Tallow Amine" OR "Polyethylene Glycol (10) Oleyl Amine" OR "Polyethylene Glycol (11) Tallow Amine" OR "Polyethylene Glycol (12) Palmityl Amine" OR "Polyethylene Glycol (15) Coconut Amine" OR "Polyethylene Glycol (15) Hydrogenated Tallow Amine" OR "Polyethylene Glycol (15) Oleyl Amine" OR "Polyethylene Glycol (15) Soy Amine" OR "Polyethylene Glycol (15) Stearyl Amine" OR "Polyethylene Glycol (2) Tallow Amine" OR "Polyethylene Glycol (20) Oleyl Amine" OR "Polyethylene Glycol (22) Tallow Amine" OR "Polyethylene Glycol (25) Oleyl Amine" OR "Polyethylene Glycol (25) Tallow Amine" OR "Polyethylene Glycol (3) Coconut Amine" OR "Polyethylene Glycol (30) Hydrogenated Tallow Amine" OR "Polyethylene Glycol (30) Oleyl Amine" OR "Polyethylene Glycol (30) Tallow Amine" OR "Polyethylene Glycol (5) Coconut Amine" OR "Polyethylene Glycol (5) Hydrogenated Tallow Amine" OR "Polyethylene Glycol (5) Oleyl Amine" OR "Polyethylene Glycol (5) Soy Amine" OR "Polyethylene Glycol (5) Stearyl Amine" OR "Polyethylene Glycol (50) Hydrogenated Tallow Amine" OR "Polyethylene Glycol (50) Stearyl Amine" OR "Polyethylene Glycol (7) Tallow Amine" OR "Polyethylene Glycol 100 Coconut Amine" OR "Polyethylene Glycol 100 Hydrogenated Tallow Amine" OR "Polyethylene Glycol 100 Lauryl Amine" OR "Polyethylene Glycol 100 Oleyl Amine" OR "Polyethylene Glycol 100 Rapeseed Amine" OR "Polyethylene Glycol 100 Soy Amine" OR "Polyethylene Glycol 100 Stearyl Amine" OR "Polyethylene Glycol 1000 Cocamine" OR "Polyethylene Glycol 1000 Hydrogenated Tallow Amine" OR "Polyethylene Glycol 1000 Tallow Amine" OR "Polyethylene Glycol 2000 Hydrogenated Tallow Amine" OR "Polyethylene Glycol 400 Hydrogenated Tallow Amine" OR "Polyethylene Glycol 400 Soy Amine" OR "Polyethylene Glycol 500 Coconut Amine" OR "Polyethylene Glycol 500 Hydrogenated Tallow Amine" OR "Polyethylene Glycol 500 Soy Amine" OR "Polyethylene Glycol 500 Stearyl Amine" OR "Polyoxyethyene (12) Palmityl Amine" OR "Polyoxyethylene (10) Coconut Amine" OR "Polyoxyethylene (10) Hydrogenated Tallow Amine" OR "Polyoxyethylene (10) Oleyl Amine" OR "Polyoxyethylene (10) Soy Amine" OR "Polyoxyethylene (10) Stearyl Amine" OR "Polyoxyethylene (11) Tallow Amine" OR "Polyoxyethylene (15) Coconut Amine" OR "Polyoxyethylene (15) Hydrogenated Tallow Amine" OR "Polyoxyethylene (15) Oleyl Amine" OR "Polyoxyethylene (15) Soy Amine" OR "Polyoxyethylene (15) Stearyl Amine" OR "Polyoxyethylene (2) Coconut Amine" OR "Polyoxyethylene (2) Hydrogenated Tallow Amine" OR "Polyoxyethylene (2) Lauryl Amine" OR "Polyoxyethylene (2) Oleyl Amine" OR "Polyoxyethylene (2) Rapeseed Amine" OR "Polyoxyethylene (2) Soy Amine" OR "Polyoxyethylene (2) Stearyl Amine" OR "Polyoxyethylene (2) Tallow Amine" OR "Polyoxyethylene (20) Cocamine" OR "Polyoxyethylene (20) Coconut Amine" OR "Polyoxyethylene (20) Hydrogenated Tallow Amine" OR "Polyoxyethylene (20) Tallow Amine" OR "Polyoxyethylene (25) Tallow Amine" OR "Polyoxyethylene (3) Coconut Amine" OR "Polyoxyethylene (30) Hydrogenated Tallow Amine" OR "Polyoxyethylene (30) Oleyl Amine" OR "Polyoxyethylene (30) Tallow Amine" OR "Polyoxyethylene (40) Hydrogenated Tallow Amine" OR "Polyoxyethylene (5) Coconut Amine" OR "Polyoxyethylene (5) Hydrogenated Tallow Amine" OR "Polyoxyethylene (5) Oleyl Amine" OR "Polyoxyethylene (5) Soy Amine" OR "Polyoxyethylene (5) Stearyl Amine" OR "Polyoxyethylene (50) Hydrogenated Tallow Amine" OR "Polyoxyethylene (50) Stearyl Amine" OR "Polyoxyethylene (7) Tallow Amine" OR "Polyoxyethylene (8) Hydrogenated Tallow Amine" OR "Polyoxyethylene (8) Soy Amine" OR "Polyoxyethylene Glycol (20) Oleyl Amine" OR "Polyoxyethylene Glycol (22) Tallow Amine" OR "Polyoxyethylene Glycol (25) Oleyl Amine" OR "Polyoxyethylene Oleylamine" OR "Polyoxyethylene Stearylamine" OR "1017280-86-2" OR "10213-78-2" OR "10213-78-2" OR "112919-11-6" OR "1174896-84-4" OR "1174896-85-5" OR "119524-12-8" OR "134665-96-6" OR "140615-76-5" OR "1416163-29-5" OR "1416163-30-8" OR "1416163-31-9" OR "1416163-32-0" OR "144840-63-1" OR "1449659-82-8" OR "1541-67-9" OR "15520-05-5" OR "160765-53-7" OR "180995-43-1" OR "18312-57-7" OR "187030-47-3" OR "18924-65-7" OR "18924-66-8" OR "18924-67-9" OR "218296-00-5" OR "233-520-3" OR "24910-32-5" OR "26635-92-7" OR "26635-92-7" OR "26635-93-8" OR "35074-73-8" OR "52891-01-7" OR "52891-02-8" OR "56049-72-0" OR "56958-53-3" OR "60884-95-9" OR "60917-33-1" OR "60917-34-2" OR "61480-62-4" OR "61670-56-2" OR "61791-14-8" OR "61791-24-0" OR "61791-26-2" OR "61791-31-9" OR "61791-31-9" OR "61791-44-4" OR "65322-67-0" OR "65482-95-3" OR "66853-72-3" OR "66853-73-4" OR "6752-33-6" OR "68155-33-9" OR "68213-26-3" OR "68308-48-5" OR "70955-14-5" OR "739328-23-5" OR "75006-50-7" OR "75006-51-8"

OR “75006-52-9” OR “7517-26-2” OR “8051-52-3” OR “82803-02-9” OR “82803-06-3” OR “82984-88-1” OR “83147-61-9” OR “84138-81-8” OR “9003-93-4” OR “92773-56-3” OR “95985-32-3” OR “98389-76-5” OR “98389-77-6” OR “99705-34-7” OR “N,N-Bis(2-hydroxyethyl)(coconut oil alkyl) amine” OR “N,N Bis(2-hydroxyethyl)(tallow alkyl) amine” OR “Tallow fatty acid diethanolamide” OR “Tallow bis(2-hydroxyethyl)amine, C 16-C 18” OR “Tallow amine, phosphate ester” OR “amines, C 13-15-alkyl,ethoxylated” OR “POE-5/POP-12 Tallow Amine” OR “ethoxylated coconut oil amine” OR “bis(hydroxyethyl) dodecylamine”

AND

1. (dermal OR skin OR (mucous AND membrane)) AND (irritation OR sensitization); 3,690 hits
2. penetration OR (penetration AND enhancer); 13,304 hits
3. toxicokinetics NOT pharmacokinetics; 179 hits
4. Metabolite NOT (bacterial OR bacteria); 33,379 hits
5. “adverse health effects”; 1,145 hits
6. (repeated OR repeat) AND “dose toxicity” 90 hits
7. neurotoxicity OR phototoxicity OR genotoxicity OR mutagenicity OR carcinogenicity OR “reproductive toxicity” OR “developmental toxicity” OR “reproductive and developmental toxicity” OR “acute toxicity” OR “subacute toxicity” OR “subchronic toxicity” OR “chronic toxicity”; 29,319
8. “effects on the endocrine system”; 35,974 hits
9. “toxicity in vitro” OR “in vitro test”; 21,857

138,937 hits, total; 4 ordered

- Scifinder – September 23, 2014
  - Search for:
    Cocamine; 83 hits
    PEG Cocamine; 23 hits
    PEG-2 Cocamine; 13 hits
    PEG-3 Cocamine; 9 hits
    PEG-5 Cocamine; 10 hits
    PEG-10 Cocamine; 5 hits
    PEG-15 Cocamine; 9 hits
    PEG-20 Cocamine; 6 hits
    PEG-4 Cocamine; 6 hits
    PEG-8 Cocamine; 3 hits
    PEG-12 Cocamine; 4 hits
    PEG Hydrogenated Tallow Amine; 19 hits
    PEG-2 Hydrogenated Tallow Amine; 2 hits
    PEG-5 Hydrogenated Tallow Amine; 0 hits
    PEG-8 Hydrogenated Tallow Amine; 0 hits
    PEG-10 Hydrogenated Tallow Amine; 0 hits
    PEG-15 Hydrogenated Tallow Amine; 0 hits
    PEG-20 Hydrogenated Tallow Amine; 1 hits
    PEG-30 Hydrogenated Tallow Amine; 0 hits
    PEG-40 Hydrogenated Tallow Amine; 0 hits
    PEG-50 Hydrogenated Tallow Amine; 0 hits
    PEG Lauramine; 54 hits
    PEG-2 Lauramine; 7 hits
    PEG Oleamine; 23 hits
    PEG-2 Oleamine; 1 hit
    PEG-5 Oleamine; 1 hit
    PEG-6 Oleamine; 2 hits
    PEG-10 Oleamine; 1 hit
    PEG-15 Oleamine; 0 hits
    PEG-20 Oleamine; 2 hits
    PEG-25 Oleamine; 0 hits
    PEG-30 Oleamine; 0 hits
    PEG-12 Palmitamine; 26 hits
    PEG-2 Rapseedamine; 0 hits
    PEG Soyamine; 2 hits
    PEG-2 Soyamine; 2 hits
    PEG-5 Soyamine; 1 hit
    PEG-8 Soyamine; 0 hits
    PEG-10 Soyamine; 1 hit
    PEG-15 Soyamine; 1 hit
    PEG Stearamine; 79 hits
    PEG-2 Stearamine; 10 hits
    PEG-5 Stearamine; 6 hits

PEG-10 Stearamine; 2 hits
PEG-15 Stearamine; 1 hit
PEG-50 Stearamine; hits
PEG Tallow Amine; 127 hits
PEG-2 Tallow Amine; 0 hits

Refine by:

1. Dermal irritation; 4 hits
2. Sensitization; 12 hits
3. Dermal absorption; 0 hits
4. Dermal penetration; 0 hits
5. Penetration enhancer; 0 hits
6. Toxicokinetics 12 hits
7. Adverse health effects; 0 hits
8. Repeated dose toxicity; 0 hit
9. Neurotoxicity; 0 hits
10. Phototoxicity; 1 hits
11. Genotoxicity; 0 hits
12. Mutagenicity; 4 hits
13. Carcinogenicity; 15 hits
14. Reproductive toxicity; 4 hits
15. Developmental toxicity; 4 hits
16. Acute toxicity; 2 hits
17. Subacute toxicity; 0 hits
18. Subchronic toxicity; 0 hits
19. Chronic toxicity; 0 hits
20. In vitro toxicity; 35 hits
21. Toxicity; 12 hits
22. Manufacturing methods; 7 hits

100 hits, total; 4 papers ordered

- PubMed – May 1, 2015 (search for papers published after September 19, 2014)
    - Search for “PEG Cocamine” OR “PEG-2 Cocamine” OR “PEG-3 Cocamine” OR “PEG-5 Cocamine” OR “PEG-10 Cocamine” OR “PEG-15 Cocamine” OR “PEG-20 Cocamine” OR “PEG-4 Cocamine” OR “PEG-8 Cocamine” OR “PEG-12 Cocamine” OR “PEG Hydrogenated Tallow Amine” OR “PEG-2 Hydrogenated Tallow Amine” OR “PEG-5 Hydrogenated Tallow Amine” OR “PEG-8 Hydrogenated Tallow Amine” OR “PEG-10 Hydrogenated Tallow Amine” OR “PEG-15 Hydrogenated Tallow Amine” OR “PEG-20 Hydrogenated Tallow Amine” OR “PEG-30 Hydrogenated Tallow Amine” OR “PEG-40 Hydrogenated Tallow Amine” OR “PEG-50 Hydrogenated Tallow Amine” OR “PEG-2 Lauramine” OR “PEG Oleamine” OR “PEG-2 Oleamine” OR “PEG-5 Oleamine” OR “PEG-6 Oleamine” OR “PEG-10 Oleamine” OR “PEG-15 Oleamine” OR “PEG-20 Oleamine” OR “PEG-25 Oleamine” OR “PEG-30 Oleamine” OR “PEG-12 Palmitamine” OR “PEG-2 Rapseedamine” OR “PEG Soyamine” OR “PEG-2 Soyamine” OR “PEG-5 Soyamine” OR “PEG-8 Soyamine” OR “PEG-10 Soyamine” OR “PEG-15 Soyamine” OR “PEG Stearamine” OR “PEG-2 Stearamine” OR “PEG-5 Stearamine” OR “PEG-10 Stearamine” OR “PEG-15 Stearamine” OR “PEG-50 Stearamine” OR “PEG Tallow Amine” OR “PEG-2 Tallow Amine” OR “PEG-7 Tallow Amine” OR “PEG-11 Tallow Amine” OR “PEG-15 Tallow Amine” OR “PEG-20 Tallow Amine” OR “PEG-22 Tallow Amine” OR “PEG-25 Tallow Amine” OR “PEG-30 Tallow Amine” OR “2,2'-(Octadecylimino)Bisethanol” OR “bis(2-Hydroxyethyl)dodecylamine” OR “Ethanol, 2,2'-(Dodecylimino)bis-” OR “Ethanol, 2,2'-(Octadecylimino)Bis-” OR “Ethanol, 2,2'-iminobis-, N-coco alkyl derivatives” OR “N,N-bis(2-Hydroxyethyl)lauramine” OR “N,N-Bis(2-Hydroxyethyl)-N-Octadecylamine” OR “N-Lauryl Diethanolamine” OR “N-Stearyldiethanolamine” OR “PEG-15 Tallow Amine” OR “PEG-2 Tallow Amine” OR “PEG-20 Tallow Amine” OR “PEG-30 Tallow Amine” OR “PEG-40 Tallow Amine” OR “PEG-5 Tallow Amine” OR “PEG-50 Tallow Amine” OR “PEG-8 Tallow Amine” OR “Polyethylene Glycol (10) Oleyl Amine” OR “Polyethylene Glycol (11) Tallow Amine” OR “Polyethylene Glycol (12) Palmityl Amine” OR “Polyethylene Glycol (15) Coconut Amine” OR “Polyethylene Glycol (15) Hydrogenated Tallow Amine” OR “Polyethylene Glycol (15) Oleyl Amine” OR “Polyethylene Glycol (15) Soy Amine” OR “Polyethylene Glycol (15) Stearyl Amine” OR “Polyethylene Glycol (2) Tallow Amine” OR “Polyethylene Glycol (20) Oleyl Amine” OR “Polyethylene Glycol (22) Tallow Amine” OR “Polyethylene Glycol (25) Oleyl Amine” OR “Polyethylene Glycol (25) Tallow Amine” OR “Polyethylene Glycol (3) Coconut Amine” OR “Polyethylene Glycol (30) Hydrogenated Tallow Amine” OR “Polyethylene Glycol (30) Oleyl Amine” OR “Polyethylene Glycol (30) Tallow Amine” OR “Polyethylene Glycol (5) Coconut Amine” OR “Polyethylene Glycol (5) Hydrogenated Tallow Amine” OR “Polyethylene Glycol (5) Oleyl Amine” OR “Polyethylene Glycol (5) Soy Amine” OR “Polyethylene Glycol (5) Stearyl Amine” OR “Polyethylene Glycol (50) Hydrogenated Tallow Amine” OR “Polyethylene Glycol (50) Stearyl Amine” OR “Polyethylene Glycol (7) Tallow Amine” OR “Polyethylene Glycol 100 Coconut Amine” OR “Polyethylene Glycol 100 Hydrogenated Tallow Amine” OR “Polyethylene Glycol 100 Lauryl Amine” OR “Polyethylene Glycol 100 Oleyl Amine” OR “Polyethylene Glycol 100 Rapeseed Amine” OR “Polyethylene Glycol 100 Soy Amine” OR “Polyethylene Glycol 100 Stearyl Amine” OR “Polyethylene Glycol 1000 Cocamine” OR “Polyethylene Glycol 1000 Hydrogenated Tallow Amine” OR

"Polyethylene Glycol 1000 Tallow Amine" OR "Polyethylene Glycol 2000 Hydrogenated Tallow Amine" OR "Polyethylene Glycol 400 Hydrogenated Tallow Amine" OR "Polyethylene Glycol 400 Soy Amine" OR "Polyethylene Glycol 500 Coconut Amine" OR "Polyethylene Glycol 500 Hydrogenated Tallow Amine" OR "Polyethylene Glycol 500 Soy Amine" OR "Polyethylene Glycol 500 Stearyl Amine" OR "Polyoxyethyene (12) Palmityl Amine" OR "Polyoxyethylene (10) Coconut Amine" OR "Polyoxyethylene (10) Hydrogenated Tallow Amine" OR "Polyoxyethylene (10) Oleyl Amine" OR "Polyoxyethylene (10) Soy Amine" OR "Polyoxyethylene (10) Stearyl Amine" OR "Polyoxyethylene (11) Tallow Amine" OR "Polyoxyethylene (15) Coconut Amine" OR "Polyoxyethylene (15) Hydrogenated Tallow Amine" OR "Polyoxyethylene (15) Oleyl Amine" OR "Polyoxyethylene (15) Soy Amine" OR "Polyoxyethylene (15) Stearyl Amine" OR "Polyoxyethylene (2) Coconut Amine" OR "Polyoxyethylene (2) Hydrogenated Tallow Amine" OR "Polyoxyethylene (2) Lauryl Amine" OR "Polyoxyethylene (2) Oleyl Amine" OR "Polyoxyethylene (2) Rapeseed Amine" OR "Polyoxyethylene (2) Soy Amine" OR "Polyoxyethylene (2) Stearyl Amine" OR "Polyoxyethylene (2) Tallow Amine" OR "Polyoxyethylene (20) Cocamine" OR "Polyoxyethylene (20) Coconut Amine" OR "Polyoxyethylene (20) Hydrogenated Tallow Amine" OR "Polyoxyethylene (20) Tallow Amine" OR "Polyoxyethylene (25) Tallow Amine" OR "Polyoxyethylene (3) Coconut Amine" OR "Polyoxyethylene (30) Hydrogenated Tallow Amine" OR "Polyoxyethylene (30) Oleyl Amine" OR "Polyoxyethylene (30) Tallow Amine" OR "Polyoxyethylene (40) Hydrogenated Tallow Amine" OR "Polyoxyethylene (5) Coconut Amine" OR "Polyoxyethylene (5) Hydrogenated Tallow Amine" OR "Polyoxyethylene (5) Oleyl Amine" OR "Polyoxyethylene (5) Soy Amine" OR "Polyoxyethylene (5) Stearyl Amine" OR "Polyoxyethylene (50) Hydrogenated Tallow Amine" OR "Polyoxyethylene (50) Stearyl Amine" OR "Polyoxyethylene (7) Tallow Amine" OR "Polyoxyethylene (8) Hydrogenated Tallow Amine" OR "Polyoxyethylene (8) Soy Amine" OR "Polyoxyethylene Glycol (20) Oleyl Amine" OR "Polyoxyethylene Glycol (22) Tallow Amine" OR "Polyoxyethylene Glycol (25) Oleyl Amine" OR "Polyoxyethylene Oleylamine" OR "Polyoxyethylene Stearylamine" OR "1017280-86-2" OR "10213-78-2" OR "10213-78-2" OR "112919-11-6" OR "1174896-84-4" OR "1174896-85-5" OR "119524-12-8" OR "134665-96-6" OR "140615-76-5" OR "1416163-29-5" OR "1416163-30-8" OR "1416163-31-9" OR "1416163-32-0" OR "144840-63-1" OR "1449659-82-8" OR "1541-67-9" OR "15520-05-5" OR "160765-53-7" OR "180995-43-1" OR "18312-57-7" OR "187030-47-3" OR "18924-65-7" OR "18924-66-8" OR "18924-67-9" OR "218296-00-5" OR "233-520-3" OR "24910-32-5" OR "26635-92-7" OR "26635-92-7" OR "26635-93-8" OR "35074-73-8" OR "52891-01-7" OR "52891-02-8" OR "56049-72-0" OR "56958-53-3" OR "60884-95-9" OR "60917-33-1" OR "60917-34-2" OR "61480-62-4" OR "61670-56-2" OR "61791-14-8" OR "61791-24-0" OR "61791-26-2" OR "61791-31-9" OR "61791-31-9" OR "61791-44-4" OR "65322-67-0" OR "65482-95-3" OR "66853-72-3" OR "66853-73-4" OR "6752-33-6" OR "68155-33-9" OR "68213-26-3" OR "68308-48-5" OR "70955-14-5" OR "739328-23-5" OR "75006-50-7" OR "75006-51-8" OR "75006-52-9" OR "7517-26-2" OR "8051-52-3" OR "82803-02-9" OR "82803-06-3" OR "82984-88-1" OR "83147-61-9" OR "84138-81-8" OR "9003-93-4" OR "92773-56-3" OR "95985-32-3" OR "98389-76-5" OR "98389-77-6" OR "99705-34-7" OR "N,N-Bis(2-hydroxyethyl)(coconut oil alkyl) amine" OR "N,N Bis(2-hydroxyethyl)(tallow alkyl) amine" OR "Tallow fatty acid diethanolamide" OR "Tallow bis(2-hydroxyethyl)amine, C 16-C 18" OR "Tallow amine, phosphate ester" OR "amines, C 13-15-alkyl,ethoxylated" OR "POE-5/POP-12 Tallow Amine" OR "ethoxylated coconut oil amine" OR "bis(hydroxyethyl) dodecylamine"

AND

10. (dermal OR skin OR (mucous AND membrane)) AND (irritation OR sensitization); 166 hits, 1 relevant (Skare et al., 2015)
11. penetration OR (penetration AND enhancer); 628 hits, none relevant
12. toxicokinetics NOT pharmacokinetics; 49 hits, none relevant
13. Metabolite NOT (bacterial OR bacteria); 2,550 hits, none relevant
14. "adverse health effects"; 205 hits, none relevant
15. (repeated OR repeat) AND "dose toxicity"; 14 hits, none relevant
16. neurotoxicity OR phototoxicity OR genotoxicity OR mutagenicity OR carcinogenicity OR "reproductive toxicity" OR "developmental toxicity" OR "reproductive and developmental toxicity" OR "acute toxicity" OR "subacute toxicity" OR "subchronic toxicity" OR "chronic toxicity"; 2,123 hits, 1 relevant (Skare et al., 2015)
17. "effects on the endocrine system"; 1,118 hits, none relevant
18. "toxicity in vitro" OR "in vitro test"; 1,834 hits, none relevant

138,937 hits, total; 4 ordered

- <u>Scifinder – September 23, 2014 (Search for papers published in 2014-2015)</u>
  - Search for:
    Cocamine; 7 hits, 1 relevant (Skare et al. 2015)
    PEG Cocamine; 3 hits, 1 relevant (Skare et al. 2015)
    PEG-2 Cocamine; 1 hit, not relevant
    PEG-3 Cocamine; 1 hit, not relevant
    PEG-5 Cocamine; 0 hits
    PEG-10 Cocamine; 5 hits
    PEG-15 Cocamine; 0 hits
    PEG-20 Cocamine; 0 hits
    PEG-4 Cocamine; 1 hit, not relevant
    PEG-8 Cocamine; 0 hit
    PEG-12 Cocamine; 0 hits

PEG Hydrogenated Tallow Amine; 0 hits
PEG-2 Hydrogenated Tallow Amine; 0 hits
PEG-5 Hydrogenated Tallow Amine; 0 hits
PEG-8 Hydrogenated Tallow Amine; 0 hits
PEG-10 Hydrogenated Tallow Amine; 0 hits
PEG-15 Hydrogenated Tallow Amine; 0 hits
PEG-20 Hydrogenated Tallow Amine; 0 hits
PEG-30 Hydrogenated Tallow Amine; 0 hits
PEG-40 Hydrogenated Tallow Amine; 0 hits
PEG-50 Hydrogenated Tallow Amine; 0 hits
PEG Lauramine; 0 hits
PEG-2 Lauramine; 0 hits
PEG Oleamine; 0 hits
PEG-2 Oleamine; 0 hit
PEG-5 Oleamine; 0 hit
PEG-6 Oleamine; 0 hits
PEG-10 Oleamine; 0 hit
PEG-15 Oleamine; 0 hits
PEG-20 Oleamine; 0 hits
PEG-25 Oleamine; 0 hits
PEG-30 Oleamine; 0 hits
PEG-12 Palmitamine; 0 hits
PEG-2 Rapseedamine; 0 hits
PEG Soyamine; 0 hits
PEG-2 Soyamine; 0 hits
PEG-5 Soyamine; 0 hit
PEG-8 Soyamine; 0 hits
PEG-10 Soyamine; 0 hit
PEG-15 Soyamine; 0 hit
PEG Stearamine; 0 hits
PEG-2 Stearamine; 0 hits
PEG-5 Stearamine; 0 hits
PEG-10 Stearamine; 0 hits
PEG-15 Stearamine; 0 hit
PEG-50 Stearamine; 0 hits
PEG Tallow Amine; 0 hits
PEG-2 Tallow Amine; 0 hits

134th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING.

Monday, March 16, 2015

Dr. Marks Team

DR. MARKS: Yeah, okay. Next is the PEG cocamine. And this really relates I think to Dr. Api's discussion this morning because a lot of what we discussed in this is - huh, how did that come there -- a lot of discussion and Ivan, you're here about the structural activity relation to face framework, so we've got -- there's a tentative amended safety assessment of the PEGs cocamine.

In December 14 meeting the panel expressed support for developing SAR-based framework safety of 32 of the 47 (inaudible) the products contained should be formulated to be non-irritating, found the information was insufficient to determine the safety of 15 of these ingredients which was X + Y less than or equal to 5, and then what we need with physical and chemical properties, genotox, 28-day dermal tox, and PEG-2 cocamine and dermal sensitization, and let me see here.

Did we get things in Wave 2? If I go to page 78 it divides it up. We did get more data on PEG-2 and 5, and then we also have an article of use of read-across for PEG cocamine's senior author as Julie Skare which the conclusion was the prediction of PEG cocamines was the same as for PEGs not present in significant concern for dermal sensitization.

So, Tom, Rons, can we now say everything safe as long as formulated to be non-sensitizing or those 15 ingredients which again is on page -- starts on page 78, that's 15 which we had insufficient before could be -- should stay that way?

DR. SHANK: Page 70 what?

DR. MARKS: Page 78 and 79 under the -- it's actually the conclusion in Ivan and said. You'll see there it lists 32 that are safe as long as being formulated to be non-irritating, and not surprising all the ones that were insufficient were less than or equal to 5, so the PEG-2 and PEG-5 basically. Cocamine hydrogenated tallow amine and we have some support here in terms of sensitization that they should be okay.

The other needs, Tom, Rons, did you feel that were okay and should we stick with this conclusion or they now all safe when formulated to be non-irritating? Let me see what other notes I have? Can we now have a conclusion for all safe, non-irritating?

DR. EISENMANN: The conclusion we would find acceptable is a three-part conclusion. The same for the PEG-6 and greater. For PEG-2 that are primarily C-18; so that would be tallow amine, hydrogenated tallow amine, oleamine, rapeseed amine, soy amine, and stearamine would like safe for use in hair dye products. Dermal sensitization data use concentrations are needed to support other uses.

And then because there's still some concerns on your part for cocamine and lauramine, that would remain insufficient with the data requests that you had previously because the data are primarily on the PEG-2 tallow amine, and so you have the dermal 28-day study and you have genotoxicity.

DR. MARKS: So you don't think we could read-across with that?

DR. EISENMANN: I think you can, but the last time -- at the last meeting it didn't seem like you guys felt you could read-across.

DR. HILL: Because we were missing some pieces of information, and we didn't have this data on PEG-2 that we now have.

DR. MARKS: Right, and actually interestingly when you look at the minutes of the Belsito team in the last time thought the SAR alone was fine with the data, so they were willing to go as safe. We wanted to see a lower one than PEG-2 which now we have, so I think we can go safe for all the ingredients.

DR. SHANK: I agree.

DR. SLAGA: I agree too.

DR. HILL: Yes, yes.

DR. MARKS: So that makes it even simpler conclusion, Carol.

DR. EISENMANN: Yes.

DR. MARKS: So who's moving tomorrow? So based on new (inaudible) safe formulated to be non-irritating? Any comments? Any other comments? Ron, Tom, Ron, Tom, anything else other than safe formulated to be non-irritating?

DR. SLAGA: No.

DR. MARKS: Okay.

DR. HILL: Just a pat on the back for Ivan.

DR. MARKS: Yes.

DR. BERGRELD: Could I just ask a question about the SAR and the Q-R? Is it Q-U-A-R?

DR. MARKS: S-A-R.

DR. BERGFELD: Well, whatever. Are we going to be applying these technical risk assessments to a lot of ingredients? I mean it was a horrendous piece of work, so it --

DR. MARKS: I like Ron Shank's comment. (inaudible) time that Ron, I'll paraphrase or do you want to put it that this is a scientific tool I think has to be rolled in. It was interesting. A presentation this morning there was at least what I took out of Ann Marie -- is she here -- that there are HRIPT and other data points that help in coming to the conclusion. That's how I view it. Ron has -- I mean to me it's another tool to use, and I like the way you phrase it. I think in here it's a framework for a systemic approach, but it doesn't stand alone in and of itself.

DR. SLAGA: Correct, and you have to have a pretty good database on (inaudible) compounds to be able to go forward with that.

DR. MARKS: I kind of look at it as being a more scientific way of how we do read-across.

DR. SHANK: Yes, it is.

DR. SLAGA: I think that's where we're going.

DR. SHANK: It will not help…

DR. SLAGA: It's a long, slow progression.

DR. SHANK: It will not help (inaudible) where you have these plant extracts. I don't see -- there's a lot more work needed (inaudible) models before you can handle mixtures.

DR. MARKS: Okay, any other comments? So, save this…

Monday, March 16, 2015

Dr. Belsito Team

DR. BELSITO: Okay. So, we are on PEGs Cocamine, right? So, at the December 2014 meeting we reviewed a strategy document, and determined the tentative amended safety assessment could be issued for the PEG cocamine and related ingredients that were greater than 5, but were insufficient for those that were less than or equal to 5. And then, subsequently, there was a huge amount of data in Wave 2, including a paper that seems to have been written and published specifically regarding the issues we are having with read across.

And since it really had been three years, I guess 2012, since we really looked at this document in any detail, I actually read the whole thing cover-to-cover again, and it looks like we were always willing to go with a safe as used conclusion, and it was the other team that was having problems with the read across for the PEGs of lower molecular weight, particularly Ron Hill.

And after reading the Skare [inaudible] paper, and looking at all the data that we had, and reading through all the discussions, I guess I'm not enough of a chemist to still understand what his concerns are, because it turns out that what's in the Skare paper is really no different from the data that we already had. Nor were the structural analogues that we had suggested be used, i.e. PEG-2 tallow amine, we looked at all of that data, there is really not a lot of new data.

So, maybe someone else can help me out, and I mean, are we, again, as a team comfortable going, safe as used? Or are we not comfortable going below PEG-6, and why are we -- if we are not, why are we not?

DR. LIEBLER: So, the last time we talked about this, that's when I think, Ron, introduced a concern regarding possible cyclization of the shorter chain length, that the short substituent, and that's supposed -- not actually the short PEGs, but the short alkyl substituent, and (inaudible) going to be going with metabolism to glucuronide or sulfate, and the suggestion that they might cyclize the reaction in the (inaudible), and it's analogous to some chemistry that is known for some halogenated hydrocarbons. But I've never heard of it with sulfated or glucuronidated intermediates, and I think that suggestion that that would be happening, in fact, that it would be at all significant, it really strikes me as pretty far-fetched. And it's at odds with the data that we do have, which I'm very comfortable with.

DR. BELSITO: Yeah, because I mean, if anything, from -- I took away, the one new thing that I took away was that the tallow amines are more unsaturated and therefore are more likely to get metabolized to toxic epoxides and hydroperoxides that would cause issues in terms of carcinogenicity or sensitization, so that using PEG-2 tallow amine, as a read across for all of the other PEG-2 amines we are looking at, would be the most conservative approach. So if we say that we can use PEG-2 tallow amine, and PEG-8 stearamine in read across, then I think we can go safe with the entire group. The one thing we are not getting would be sensitization data, and quite honestly these are going to irritate before they sensitize, and I had a hard time interpreting the LLNA data because I think a lot of what we are seeing in terms of SI was irritation, and not sensitization, so I'm really not concerned about any of these. And then on top of it, the lower molecular weights, the ones we are saying are insufficient are all in rinse-off hair coloring products.

DR. LIEBLER: Right.

DR. BELSITO: Now I didn't buy PCPC's argument that they are exempt because of the labeling to patch test, because it's not clear to me -- Is everything in a hair dye exempt? Or is it only the coal-tar derived ingredients? I read the law as being coal-tar derived ingredients, not anything else you throw in. But having said that, since their use is only in rinse-offs, and I think even in leave-ons that use will be limited by irritation before you get to sensitization, I have no problem.

DR. ANSELL: We agree.

DR. LIEBLER: So, we can basically get the same result without invoking the coal tar kind of language, the patch test language?

DR. ANSELL: Yeah.

DR. LIEBLER: We are simply saying, safe as used in hair dyes when (inaudible)?

DR. BELSITO: No. Safe as used when formulated -- safe as used when formulated to be nonirritating.

DR. LIEBLER: Period?

DR. BELSITO: Period.

DR. LIEBLER: Okay.

DR. BELSITO: Because they are used below -- even is hair-coloring products only, right, but certainly five and less was all hair coloring.

DR. LIEBLER: Yeah.

DR. BELSITO: We've got -- I think we've got enough data table of use here, right?

DR. BOYER: Yeah. Actually it was Wave 2 memo that does provide somewhat of an update.

DR. BELSITO: Yeah. That's what I'm looking for.

DR. BOYER: It's not a huge change.

DR. BELSITO: Yeah. It's here. It's Table 7 in Wave 2, so you have the originals. Table 7 is the originals. PEG-2, 3, 5 are only, and then Table 8 is the others. PEG-5, hydrogenated tallow is hair coloring one. PEG-8, hydrogenated tallow is hair coloring; and then PEG-2 is hair coloring, PEG-2 oleamine, PEG-2 rapeseedamine is hair coloring, PEG-2 soyamine is hair coloring, PEG-5 soyamine is hair coloring, PEG-2 tallow amine is hair coloring. And then all of the others, PEG-3, 4, cocamine aren't used, and then the next is PEG-8 cocamine that's not used. So, you know, everything, 5 or less, is all hair coloring rinse off. So that's where I was.

DR. LIEBLER: I agree.

DR. BELSITO: Okay. Paul?

DR. SNYDER: I agree.

DR. KLAASSEN: And I agree.

DR. BELSITO: Okay. So then let's look at the paper. Obviously under the application of the framework to evaluate PEGs cocamine, we need to add in Julie's reference that's now been published, and probably we can eliminate all of the synopsis of what went on in our Panel Meeting and just reference that paper.

DR. BOYER: Absolutely.

DR. BELSITO: That will shorten the document. I think that we need to point out in the application of the framework, very importantly that, you know, again the PEGs tallow amine, are more unsaturated and they are more likely to produce epoxides and hydroperoxides, and therefore they conservative read-across group.

In terms of the nitrosamines, I would assume that PEG-2 tallow amine would have roughly the same amount and so that the 90-day oral with the PEG-2 tallow amine would suffice for any concerns we might have about carcinogenicity from nitrosamines with PEG-2 cocamine or any of the other PEG-2 derivatives. That would go in the discussion.

And under, I guess, are we -- we go under impurities. The 28-day dermal toxicity we have for PEG-2 tallow amine, and you know, so we've sort of met that request, and again we don't need the dermal sensitization because these will irritate well before they sensitize, and they are used in wash-off products, not leave-ons at that low concentration; so all of that would go in the discussion. And I think that's all I have comments for a final document to go out as a tentative final. Paul?

DR. SNYDER: So this was a tentative amended final, so we are okay?

DR. KLAASSEN: Well, it's a draft final amended report, so if the Panel agrees that with -- upon a conclusion, the overall conclusion, both teams, it would go out as a final.

DR. SNYDER: Okay. So we'll see it one more time as a final?

DR. BELSITO: Yes. Yeah -- No -- because if it had gone out, if we are changing --

DR. SNYDER: Insufficient?

DR. BELSITO: No. If it had gone out with -- this was a final, tentative final --

DR. SNYDER: Okay. That's what I was asking.

DR. BELSITO: -- that we are now changing the conclusion. So it will have to go out as a tentative final again. So we will see it again.

DR. SNYDER: See it one more time. Okay.

DR. BELSITO: Right?

DR. LIEBLER: Right. Right.

DR. BELSITO: Okay. Well, we'll see what the other group says, but Dan, I'm counting on you to be my point man for any objections that Ron has, because I couldn't follow his objections after looking at all those.

DR. LIEBLER: Right. Yeah.

DR. SNYDER: Plus all the read across stuff.

DR. BELSITO: Yeah. They were objecting to, but I mean, short of the fact that the -- at least for me -- short of the fact that the tallow amines are unsaturated and are more likely to be metabolized to more "toxic" in quotation marks, metabolic byproducts like epoxides and hydroperoxides, it was nothing new to me, and all the information we got, than what we had in 2012 and in December of last year.

DR. LIEBLER: Right. I mean, these things are pretty -- these things were clean for genotox?

DR. BELSITO: Right.

DR. LIEBLER: And so the argument -- the argument for the kind of activation to reactive intermediate, that Ron mentioned earlier, that's a reaction that's associated with genotoxicity, and sort of clean for genotox.

DR. BELSITO: Okay.

DR. LIEBLER: And I think the thing that I hadn't quite picked up on, it was the degree of irritation confounds the sensitization experiments to the point that you really can't an unambiguous conclusion about sensitization, so if you formulate to be nonirritating you -- and that these short ones are used in hair dye product rinse offs, I think we are fine.

DR. BELSITO: Okay.

DR. LIEBLER: I don't think there's much of chemical argument to make.

Tuesday, March 17, 2015

DR. BERGFELD: Well, thank you very much. We're going to then move on to the report and the final reports are the first up. Dr. Belsito will be reporting on PEGs cocamine.

DR. BELSITO: The PEGs cocamine related ingredients. So in December we reviewed the strategy document --

DR. LIEBLER: Your mic.

DR. BELSITO: It's on. At December we reviewed the strategy document, determined that a tentative amended safety assessment report could be used based upon data and structural activity relationship-based read across analysis presented. We received in the initial wave one a draft and in a subsequent wave, an actual published paper by actually Skare, the people at Proctor & Gamble, looking at this. And other than for that, we also received comments from Personal Care Products Council correcting certain elements of the document and some updates on concentration of use in cosmetic products.

I think as you recall, my team actually was willing to go with a safe as used across the board for all of these in December. And after re-reviewing all of the data and the and the Skare paper, we still felt that we could go safe as used. We thought that PEG-2 tallow amine was more than an adequate read across, particularly since the tallow amine is more unsaturated and more likely to form epoxides and hydroperoxides that would be more sensitizing. There was really no genotoxicity. We assume that the amount of residual nitrosamine would be similar in both of the products. We really didn't see any alerts coming up there. And we would actually move to change the conclusion, particularly in light of the fact that everything five and below is used in a rinse off hair coloring no higher than 35.5 percent. So we would move that they are all safe as used.

DR. MARKS: We concur. We wondered whether it should be formulated to being non-irritating.

DR. BELSITO: Yes.

DR. MARKS: Thank you. So the move is safe formulated to be non-irritating. We second that.

DR. BERGFELD: Is there any further discussion?

DR. BELSITO: Yeah, well, we're lacking sensitization data. But these are irritating, and they're going to irritate well before they get to sensitization. And I think that that was shown in the LLNA where the data was very difficult to interpret, and you oftentimes see that when you're testing materials that are close to irritation. I think in the discussion we need to point out about the tallow amines being more unsaturated and therefore a very conservative estimate in terms of potential toxicities of the other related ingredients in here. And that was basically it.

DR. BERGFELD: Any of the other panel members wish to add to this? Dan?

DR. LIEBLER: Yeah, I just have one comment. In the discussion, based on a point I think that Ron made, Ron Hill made it in our discussion last time on the PDF page 78, the one, two, three, fourth paragraph down. There's a line about some of the molecules may be primary or secondary means that may be glucuronidated or sulphated and undergo intermolecular cyclization to yield potentially sensitizing electrophilic quantized intermediates. You know, I think that's pretty speculative for these. We really don't have any evidence that this would happen. And the molecules that are relevant at least where we have genotox data or mutagenicity data are negative. So I would suggest that that phrase be taken out. I think it's applicable to dibromoethane, but not in this case.

DR. HILL: I'm comfortable with that. As you remember, we did not have the data, any data for the low molecular weight substances at the last meeting, and now we do have results for PEG 2 tallow amine, which increases my comfort level a lot. So yes, I'm fine with having that stricken.

DR. BERGFELD: Okay, so it's stricken. Any other comments or edits? Seeing none I'll the question, all those in favor of approval, please raise your hands. Unanimous, thank you. So moving to the second ingredient then, ceramides…

133th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING.

Monday, December 8, 2014

Dr. Marks Team

DR. MARKS: So, you heard earlier, Dr. Ron Shank is not going to be here with us today. So what I will do as we go through the ingredients, Ron Shank sent me his comments on the readings. They are, by and large, pithy, so it won't take long to read his comments. And then perhaps later on today if we need some clarification I'll give him a call.

So, the first ingredient we have, are the PEGs cocamine and related ingredients. Ivan, you are the writer of this. And just to review, since it's got some history here, in 1999, an insufficient data conclusion was rendered. And just to repeat those, data needs, physical chemical properties including impurities, genotox and mammalian test system; and if positive, dermal carcinogenesis study; 28-day dermal tox using PEG-2 cocamine, and dermal sensitization data on cocamine. So, PEG-2 cocamine was an important ingredient to be able to read across.

In 2012 these ingredients were reopened. Our team actually then, when I read the minutes, thought that we could move on, and felt that they were safe; but subsequent to that we had a robust QSAR presentation, and I think the issue today is, can we use the QSAR to read across for the PEG-2 cocamine and the other ingredients, are all the add-ons okay, and how should we proceed? And then do you want to illuminate that?

DR. BOYER: Yes. And actually it's not -- the emphasis isn't really on QSAR, meaning quantitative structure activity relationship analysis. It's more -- what we are trying to do is implement what is referred to as a framework for identifying analogs, for evaluating analogs for read across. And it's a very flexible system that enables the incorporation of information from multiple sources.

It can be actual study data, test data, and so forth and can accommodate QSAR analyses and other types of evaluations, to more or less support an overall weight-of-evidence analysis and weight-of-evidence conclusion for ingredients, for a group of ingredients. And so what you have before you, what's been summarized in the strategy memorandum, is basically a run through of all of the information and the analyses, including a few QSARs, QSAR analyses which don't really play, necessarily, a central role, and certainly don't carry a whole lot of weight by themselves.

But it's really a matter of looking at the total picture, across the toxicological endpoints; across results, outcomes of various analyses of which there are maybe one or two QSAR exercises that were implemented. It's a way of looking at all of the information that's available for the -- what we refer to as the structure of interest -- that would be the structure for which we want to do read across.

And looking also at selecting specific analogs and looking at all of the data that's associated with the analogs as well, and seeing how, ultimately, all of that information about metabolism, chemical properties, toxicity, and so forth, reactivity, how all of that forms a coherent picture that enables the data gaps to be filled, that supports that kind of evaluation.

So, we are really more or less in an interim period with respect to the development of these kinds of approaches during read across, going beyond simply reading across data that might be available for some ingredients, and an

ingredient group, across the entire ingredient group, toward bringing in information, toxicological information, property information, and so forth, from other substances that are simply not ingredients, but for which the information can be valuable, can be incorporated into an overall weight of evidence analysis centered around a read-across approach.

So it's really a structure-activity relationship approach, it's -- right now we're not -- we are not doing a whole lot of QSAR, although that certainly is the hope for the future, that at some point we'll be able to make use of those kinds of analyses to good effect as well.

DR. MARKS: So on page 129 you summarized the questions, do the selected analogs adequately cover the chemical space, or the tox studies that are summarized in Tables 5, 11, sufficient. The next bullet was; concordance, consistency as they are sufficient -- concordance and consistency, and it's the read-cross analysis. Okay. Does it support?

So let me next read Ron Shank's comments. PEGs cocamine, "I think we need clear input from the chemists as far as read across is concerned, for adding the remaining PEG aliphatic amines from other lipids. I like the SAR models for research purposes, but am not yet ready to recommend them today for using safety assessment on widely-used chemicals. If the panel concludes the PEG cocamine data are still insufficient, I don't recommend opening the report to add anything else unless the new ingredients can be used for read across to remove any concerns about PEG-2 cocamine." So, Tom and Ron Hill?

DR. SLAGA: I totally agree with what Ron Shank. I you know -- if we had data to support the PEG cocamine 2 from the other compounds that they want to add then I would say, let's go ahead, and we could finally end this long courtship with this compound or group.

DR. MARKS: So you would suggest not to reopen it?

DR. SLAGA: I would say that's --.

DR. MARKS: Because you don't feel like, even with the SAR we don't have enough data that we could read across the PE-2 cocamine and then feel safe with the add-ons?

DR. SLAGA: Ron?

DR. HILL: There are most definitely new issues that are created by adding some of these ingredients. If he's saying, are we looking -- do we have sufficient information to put the add-ons in there, then I think, in my mind, the answer is no. And I have a list of issues if we wanted to do that. But I don't know where these are in terms of -- I need to remind myself which ones have been reviewed, versus have never been reviewed, versus have been reviewed some years back. So, I need to be looking at that table again.

DR. MARKS: I don't think we have that usual table in here other than where -- where is read with (inaudible), and it's been looked at for each ingredient and which ones are new. Jay, did you have any comments from that?

So at this point it looks like we are going to -- I will be making a motion tomorrow not to reopen, that we don't feel comfortable with a read across for PEG-2 cocamine based on the SARs, and then therefore, if we don't reopen, we don't have to even be concerned about add-ons.

DR. ANSELL: You know, I think the -- Council's position has been clear over to years that we strongly support the use of integrated assessments. Which include not only the toxin data on the compound of -- under compound of interest, but also other data that may be derived from in vivo, in vitro or in silico methods.

We, also, through the CSSC have looked at some of the add-ins and feel, for example, that the tallow amid, the phosphates probably have gone a little far. But in terms of the conclusion we think -- we agree that PEG-2 probably falls outside of this family. So to the extent that we had a conclusion as it relates to PEGs greater than 15 and rinse-offs less than 15, excluding PEG-2, that would be acceptable for us as well.

DR. MARKS: Okay. So I think the problem with that, at least the way we -- it sounds like, Tom, Ron, we all agree with that, with the Committee's approach too. I think in the standard operating procedures if we reopen something and it's not really an add-on -- a no brainer -- then we would not reopen it. I mean we would have to reopen it then to say, delete cocamine 2 and -- or PEG-2 cocamine, and then move on with the rest of the ingredients. I don't think we are prepared to do that.

Does that sound -- Ron and Tom? And I would make a motion not to reopen, and then there would be a robust discussion about how we don't feel comfortable with a safe read across for PEG-2 cocamine.

DR. ANSELL: Then I would just since -- if we are going in that direction I would just say we need to include PEG-4, at least in that assessment because -- PEGs-4; there's more than one compound -- because PEG-4 represents the distribution, so on that small end there can be some compounds where there are hydroxyethyl chains, as opposed polyethylene glycol type chains, and we would need to be able to capture the toxicology there that overlap the PEGs-2, I think.

And then the other thing about stearates versus some of these others is, the lack of unsaturated side chains, and there were some issues related to that that we hadn't discussed much that came to mind, not the least of which was the possibility of creating trans fatty acids that could then be hydroperoxidated, or lipid peroxides that could lead to sensitization. I'm not sure that we have enough toxicology data based on the summary that was there. That doesn't we shouldn't and couldn't [ask for] it.

So, I mean, I guess basically it's if we reopen we'd be looking at an insufficiency of information for some of these things, and again, I half-made a list of the things I thought I'd be looking for.

DR. MARKS: Okay. We can -- you can either mention that tomorrow, Ron, and as we get into the discussion point give that to Ivan. But -- so tomorrow, Tom and Ron, I'll move that we not reopen, and the significant reason is that we don't feel that we can come to a safe conclusion with an SAR read across for PEG-2, and also for PEG-4 as you mentioned here.

DR. HILL: And just, as well, to remember that those PEGs represent a distribution; and on the low end we can have 1 plus 3, as well as 2 plus 2 and like that. so. And then one idealized structure; and that -- with the QSAR that was one of the things that I thought was big limitation, was that we are plugging in just one compound structure, when in reality we need a multiplicity to do the calculations on if we are going to go that route. And in the meanwhile, I'll familiarize myself much better with some of these computed end points in terms of their scope of applicability.

And also the breadth of case reports that was in that cross rack, I keep -- and I'm going to shut up here in a second; but the breadth of case studies that was in that report, I mean there's a pretty good representation, but it's certainly not all comprehensive. And it's also well to remember that in computation work, that when we are interpolating we can feel way more comfortable than we are extrapolating on certain issues. And that's the other thing to --.

DR. BOYER: Okay. But since the QSAR plays, It can play actually a small role in this particular analysis.

DR. HILL: I agree.

DR. BOYER: Can we get the Panel's opinion about the overall strategy, the implementation of the framework? Is there any reluctance to identifying analogs that may not be cosmetic ingredients, that we can bring them into -- that would enable us to bring toxicological information into the -- the assessment of the group of the ingredients.

DR. HILL: I guess I thought we'd been doing that to some extent all along. For example, on one of the reports today I'd asked for information on -- I think it was on decanoic acid. And decanoic acid when we did it, we hadn't captured that before, and there's commentary in the reports, so I thought -- I thought we had been doing that to some extent all along. You all have seemed to be drawing the line, well, if it's pharmacology, if it's drug-like action, we don't always bring that into consideration; whereas, I'm always stumping to do that. But when it's within realm of the concentrations we might develop in vivo by some cosmetic use, I think you do consider whatever biology is known.

DR. BOYER: Right. We do that, but we don't identify the analogs in a computational manner. It's a very systematic manner that's laid out in this particular framework. I think that's what we are trying to introduce into the process, is this very systematic approach. It's not dependent necessarily on QSAR, with that kind of computational analysis; although, you know, if you are looking for structures that are similar on many different levels including potential for toxicological [effects], and so forth, and properties, there are some fairly well-accepted computational tools that would unable us to do that.

So that we can extend our search for toxicological information beyond -- I mean, just starting with a group of ingredients and then searching for structures that are likely to enable us to bring toxicological information into the overall analysis. And I think this is more or less the first time that we've attempted that particular way of doing things.

DR. HILL: In terms of formalizing the strategy?

DR. BOYER: Right.

DR. HILL: I think the biggest thing to remember on any computational tool is that boundary conditions matter a lot in the sense that -- especially when they have been created and validated with certain assumptions it's crucial to know what those assumptions are in terms of how far you can take the data and interpret it.

DR. MARKS: Right.

DR. HILL: So when we make use of these tools we'll have to become at least somewhat or somebody -- I'm feeling a great weight on my shoulders here from this; but to become sufficiently expert in that range. Or, I think, more importantly, solicit some outside expertise when it's crucial to know, to be sure that we are not overextending those boundary conditions. Because if you take metabolism, for example, biotransformation, a tool that's designed to predict, that, first of all, honestly. we are still not that great at it.

I mean we can -- I can look at structures and say, I think this will happen or that will happen, but then the reality is the trafficking in an organism matters a lot in terms of what actually does appear, and I'd always prefer data of some sort. Ideally human data of some sort, which is usually not available, to get a more solid picture, because metabolism that occurs in one tissue can result in toxicology in another tissue. Which is always a limitation with in vitro models, period, but then animals aren't humans either.

DR. BOYER: Right.

DR. SLAGA: It's always nice to have a little data.

DR. ANSELL: Well the -- I guess to this specific case, to the extent that you feel uncomfortable with the extension of the family, I think that's fine. To the extent that Ivan brings up, to the framework, I mean, we strongly support this framework. I mean this is --.

DR. HILL: So do I; I'm not -- I didn't want to say that I didn't.

DR. ANSELL: You know, and we are not --.

DR. SLAGA: No. I don't think any of us said that we didn't, it's just that --.

DR. HILL: Well, I want it to be clear that I did.

DR. ANSELL: Yes. Okay. And I just want tomorrow that to be clear because that's a fundamentally different conclusion as to whether we think two is in or outside the envelope, than we are uncomfortable with the use of computational methodology. The computational approaches clearly are not black boxes that can be -- or they are not black boxes to the extent that the conclusions do not require expert assessment.

You know, we all recognize that, but the use of these computational methods is becoming more and more robust that the models are better and better. And they are clearly where we are today; the use of integrated assessments, we are using all of the data that's available. And structural alerts, structural analogs are all part of that.

DR. MARKS: Well, is this driven, Jay, to a certain extent by the -- both the direction and the regulations that prohibit animal testing?

DR. ANSELL: Right.

DR. MARKS: And so therefore you need a substitute way or surrogate way to determine safety?

DR. ANSELL: If I may get on my soapbox, no.

DR. MARKS: No.

DR. ANSELL: This is better science.

DR. MARKS: Okay.

DR. ANSELL: If we were to design safety assessment today we would not start with animals. We would start with understanding that the activity of the materials at the molecular level. Now, it is a challenge today but, you know, historically, the assessments we've used through the 20th century are full of a whole series of political compromises, social compromises. No one has ever validated that animals are relevant to human assessment, we just accept them.

Today we are starting to develop an understanding of the mechanisms at the molecular level. And so it's not second-best, it is actually a much better approach. It is better science and, you know --.

DR. MARKS: Yes. I didn't want to imply it was a second --.

DR. ANSELL: Well, no. It's often -- it often comes and people start with well, you know, you are committed to doing away with animal models and that's true. But I think one of the things that's held us back is this idea that we need to validate the in silico methods against animal models; that the computer method is exactly the same method that the animals would give; but, we've never validated the animals.

DR. SLAGA: That's right.

DR. ANSELL: So what we would like to do is to --.

DR. SLAGA: To humans, we haven't, that's right.

DR. ANSELL: That's right. So what we'd like to talk about is the role within safety assessment.

DR. SLAGA: And I think the framework that Ivan has thrown out is definitely the direction that toxicology is going.

DR. ANSELL: Yes. And there's no doubt molecular understanding is very important; and through that, even the animal models that are used, especially in cancer research, they're all humanized, if we can use that word. And it's all because of our molecular understanding. So you put the things in to make them more like the humans, and therefore they get the same tumors, that the humans get. So, at that point, we are going in that direction.

DR. GILL: And that's come -- that raises for me a question. You mentioned, it's always nice to have a little bit of data. And what we were discussing and wrestling with internally is; what's the mood of the data and what's that gap in the data that we need to have to feel more comfortable with using this. I don't expect that answer today, but it's something that I think we'd like to work more with the Science and Support Committee as we work through how to bridge that gap -- data that would make -- feel more comfortable in using this model.

DR. MARKS: I guess, this ingredient would be page 83, it doesn't sound like the -- we don't feel comfortable using SAR to meet the data needs that were outlined there, in the four bullets. I don't think anything -- and I bring that up so that, you know, when we don't reopen it, if you go back and say, well, do we need those four bullets or how much of that can be answered by an SAR analysis.

DR. ANSELL: And not to, you know, be too (inaudible), too pedantic but I think --.

DR. MARKS: No. That's okay.

DR. ANSELL: -- I think what we are saying is PEG-2 falls outside the family. And that's always been our argument, is that we can put multiple families into a report, but the data on a material should support all of the members of that family. And what we are saying, I think, is that PEG-2 is not a -- you know, should not be -- the PEG -- the PEG-15 data does not support PEG-2.

DR. MARKS: Right.

DR. ANSELL: And I think we agree.

DR. HILL: And I would argue, it does not support PEG-4 as well, although we have some PEG-4 data on one compound, so.

DR. BERGFELD: As a clinician, I want to ask a question. How do we figure out which one falls outside the family?

DR. HILL: You've got to have a PhD in Medicinal Chemistry and a lot of years experience in (inaudible) for chemical toxicology, but I mean they actually say that in one place and so -- because that's what we got from the presentation that Proctor & Gamble made. But that's a specious argument, because even in the drug realm when you get a bunch of different medicinal chemists, it's been documented in the literature, and take their opinion, they frequently don't agree on a whole lot.

So, I mean, the harsh reality is, you need these computational tools, and we need to know what the boundary conditions are to even make those decisions. And I think that's part of what this was about, was figuring out, then how do we bring that all to bear.

DR. ANSELL: But the computation was just a data point.

DR. HILL: It is a data point.

DR. ANSELL: In the case of PEG-2, we know the materials are irritating, it's not used. So from our standpoint --.

DR. BERGFELD: So it's a human experiment; so an animal experiment?

DR. ANSELL: It's the integrated assessment. And that can come from, you know --.

DR. BERGFELD: So you cannot totally replace this new formatting with what is available now with animal and human testing?

DR. ANSELL: Well I'm not sure that that's what Ivan was arguing. Right?

DR. BOYER: No.

DR. BERGFELD: Are you are talking integrated use at all?

DR. BOYER: Basically you are using all your -- you're looking at all of the toxicological inference that you have information for, for both the structure of interest as well as all of the analogs that you're -- that the medicinal

chemist typically selects to begin with. And looking for, you know, the uniformity in terms of the results of those kinds of tests -- looking for similarities among the various structures on many different levels. And where you see concordance that gives you strength; that reduces the uncertainty in what it is that you are doing, the exercise that you're undertaking. Once you've come to that point you can then feel fairly comfortable filling gaps with the information that you do have across the board.

DR. HILL: And I think one way of answering that is that we -- when I'm looking at something I'm trying to make those decisions based on heuristics of all the years of looking at how does chemistry relate to biology, but realizing that every time I see a new set of ingredients that's not anything like what I saw before; okay, if they are all molecular weight, 100,000, and I don't think there's anything problematic with accumulation and [inaudible] for something like that, then in general I'm not too worried that I'm looking for anything of low molecular weight.

But saying, oh, that biology belies the fact that I'm surprised about every other day with some new aspect of the way that molecules interact with biology; so one way of answering the question is, it's going to be a rapidly-evolving landscape for the foreseeable future. And perhaps even more rapidly year-by-year; because, well we are learning about biology, which then feeds back into how would that relate to this particular ingredient. So I mean I'm -- this has been more humbling; I've always been humbled by developments in biology and chemistry, but this has been more humbling by several orders of magnitude. Okay.

DR. BOYER: Did you -- did you find the computation of -- the prediction of metabolites from PEGs-4, did you find that to be helpful in any way? I mean, basically what they did was they plugged in a specific structure for PEGs-4, and they generated 10 or 11 or 14 different metabolites including intermediate metabolites and so on. You know, my take on an exercise like that would be for a medicinal chemist to take a look at the output and see whether or not it's reasonable, whether or not it pretty much covers all of the plausible basis, and so forth. Did you find that to be helpful in any way?

DR. HILL: Yes. However, covering all the plausible possibilities doesn't give you comfort as to what's likely to happen based on lack of knowledge of how these things might be trafficked. So in order, for example, to be metabolized by P450s, compounds have to get into metabolites -- or get to hepatocytes, or any other cells where those P450s are. And then how do they get into the cells, because if it's going through some sort of a membrane-based internalization process, and we've got molecules being chewed up in lysosomes that may end up being -- at dead ends of being a fairly different circumstance, than if we have something directly diffusing in.

Or, you know, if there's a transporter of some sort, or there's not. So you ultimately would like to have -- unfortunately, we are creating things like artificial livers where you can do -- it's not just liver, and it doesn't tell us about skin. So, I keep looking for data. We have a lot of gaps in our knowledge about biotransformation and skin. We are getting there, and I suspect that there are companies in the world that know a lot more about this than what's been published in the open literature, I suspect. But the more of that that comes out, the better we can make some guesses as to what's reasonable or not.

Because I looked at a lot of these metabolites, and I could say, well that's not going to happen, or no, all the action is going to be on the other end. Probably, you know, based on the fact that it's going to look at this as an unsaturated or a saturated fatty acid and so forth. But how does that little PEG on the other end affect the way that that -- you know, will it get into the mitochondria? Will it undergo beta oxidation cycles? Or, is it totally excluded? And those kinds of questions, you need some experiment, to run the data.

DR. BOYER: Right. On the other hand, it's probably more important -- I mean if you get you get a prediction, you get an outcome that basically covers a lot of -- a lot of space and, you know, you can as a -- with your experience and knowledge, and so forth, you can eliminate certain --.

DR. HILL: Yes.

DR. BOYER: -- at least predicted metabolites. But it would be more important to look at it from a point of view of, are there any likely major metabolites that didn't appear?

DR. SLAGA: I think that's very useful.

DR. HILL: And in that particular analysis, for example, I was looking and saying; well, if we make a glucuronide or a sulphate, there was a very real possibility that we can get intermolecular cyclization on some of these, and make reactive intermediate because then we've got to quaternize nitrogen. And none of that was actually captured by these predictions; and knowing what I know about drug metabolism those things happen. You see them. You actually see them and they have toxicological relevance, and so --.

DR. BOYER: Okay. So that kind of analysis, answers to those types of questions, I think would be very helpful to us to enabling us to --.

DR. MARKS: And Ivan, what I would suggest also, what Ron Shank said, is he likes it as a research tool at this point. So perhaps a conversation with him would be good to get his perspective also I think, one-on-one. I'm not sure I'll call him this afternoon because I don't think it's going to change our conclusion. And it's interesting I always hesitate to prolong things. But I'll raise the question. One could be -- and Lillian, this is really directed to you. Could these ingredients be reopened with the purpose of dropping PEG-2 cocamine, PEG 4 to PEG-3 in the next rendition, use the SAR to the support read across. And, you know, look at the add-ons more closely since as Ron Shank -- Ron Hill said and I don't -- I can't remember whether we've reopened the delete ingredients, but --.

DR. BERGFELD: I have it reopened.

DR. MARKS: Yes. So that's why he asked whether -- and I guess I would ask Industry to propose that if they want to in the future.

DR. GILL: Well, one other question to that; and I think -- I was thinking the same thing. Is there enough, if those two came out, or three came out, that will make the Panel comfortable? And if not, what other kinds of data information would you need? Because I would hesitate to bring it forward, or Industry may hesitate to bring it forward, if there were still some questions.

So, whether or not it comes -- they open it for the next round, I would encourage us to take those out and see what kind of information is needed, and whether or not we can address some of Ron Hill's concerns that I heard earlier. I don't know. I think it's a good -- it's a good approach to keeping it moving. And in the vein of Ron saying it's a good research tool, in some circles, particularly government, they call it a good pilot tool. So it may be a good place to start looking at these; as what's the potential if you take the two and the four out?

DR. MARKS: Well I think, tomorrow what I will do is see what the Belsito Team have done, and how they come through. But I'll still move not to reopen; still not safe with SAR read across for PEG-2 cocamine. We support the SAR framework, and as a useful toxicological, or a useful tool for reviewing toxicology. And then perhaps in the discussion, if it comes up, reopen, delete, I think our team could support that.

What do you think, Ron and Tom; as an alternative? Not only set a precedent with using SAR in the framework you're talking but maybe setting a precedent of reopening and maybe deleting ingredients.

DR. BERGFELD: We have to look at the regs, the administrative regs.

DR. GILL: I don't think we can reopen to delete, I think it's reopened to (inaudible) to add.

DR. ANSELL: Well, it's actually -- it's --.

DR. SLAGA: Is it that hard to put date on there too?

DR. ANSELL: -- it's going to appeal.

DR. HILL: I don't think you -- not going to give me any data on the two, because –

DR. MARKS: It's an irritant.

SPEAKERS: (Inaudible).

DR. GILL: So we can always give a decision without those two? I mean the panel often says we are comfortable with the data for whatever number of ingredients, but not for two others. So since it's in -- Ivan, Thanks for reminding me it's already been reopened.

DR. SLAGA: It's -- right now the status is reopened?

DR. MARKS: Yes. We are going -- I'm going to move tomorrow not to reopen. Now the other is rather than delete is as we've done in reports previously, we can say the majority of the ingredients are safe and two are insufficient.

DR. ANSELL: I guess I'm looking to Lillian. My notes didn't suggest this was a reopened discussion?

DR. GILL: No. This -- And that's why we didn't bring it as a report, an assessment. It was brought as a discussion.

DR. ANSELL: Ah! Okay.

DR. SLAGA: This is a strategy-owned.

DR. GILL: A strategy --.

DR. ANSELL: Well, you know, I think --.

DR. MARKS: Don't you think we can move on? Because we did reopen it in one of the procedures, we can, after we've looked at it, reopened, we can still close. We don't have to move forward, we can just say, no, we don't --.

DR. BERGFELD: You are saying it wasn't ever reopened?

DR. MARKS: No. No. It was reopened, but we decided not to proceed, so we closed it.

DR. GILL: It's a little confusing because it's a strategy for discussion. But at the end of that we say, whatever the Panel decides to do. It could be a tentative report if the Panel says, and we don't want to move forward with the report.

DR. MARKS: So the other option would be to move forward with deleting -- not deleting -- with declaring several of the ingredients insufficient. Is that, Tom and Ron, so an option?

DR. HILL: If you think it's going to go that way, then I need to be sure I know which ones are insufficient overnight. Then I could to do that.

DR. MARKS: Yes, roughly. We'll be back at -- we'll be back with this.

DR. HILL: But we haven't done a tentative report yet, right?

DR. MARKS: No. Ivan was mainly the -- presenting the approach with the SAR here, and the grouping, and so on.

DR. BOYER: One other question has for Dr. Hill. It has to do with the use of the Tallow Amines as its, as analogs for the PEGs cocamine. The argument that's presented is that in fact because the tallow amines tend to be unsaturated, that including them as analogs in the assessment of PEGs cocamine, is actually a conservative approach.

DR. ANSELL: It is a conservative approach.

DR. BOYER: So you found that to be convincing.

DR. Hill: Well, no. And actually the cocamine has some -- if I've calculated right, well 11 percent unsaturated, or something like that. There's a significant fraction of unsaturated. So my thing was using stearmine to read across, the cocamine didn't make good sense because we might be missing anything related --.

DR. BOYER: But do you see -- do you see if, in fact, we decide not to include the tallow amines among the ingredients into this particular report, do you still see some value in bringing the toxicological data from those ingredients into the assessment of PEGs cocamine?

DR. HILL: Yes. Yes. Yes.

DR. BOYER: Okay.

SPEAKER: Dr. Marks, I --.

DR. STEINBERG: Just want to comment --.

DR. MARKS: Just about -- hang on to that.

DR. STEINBERG: Okay. Cocamine or coconut fatty acid covers a multitude of sins because of the INCI Nomenclature, and it can be fully saturated so there's no (inaudible) present, and still be called cocoa, and so -- or partially hydrogenated. There are all sorts of variations of the same thing. So it's the composition which I think you should be really asking, as opposed to just lumping all cocoa or stearyl being fully saturated or unsaturated. The same with tallow, hydrogenated -- there's partially hydrogenated tallow fatty acids available (inaudible).

DR. HILL: Well, right. And then that raises, again, with partially hydrogenated, you know, then --.

DR. STEINBERG: Instead of (inaudible)?

DR. HILL: -- if we captured iso/trans, what happens to those? And does that matter? It may not.

DR. ANSELL: From a framework standpoint those are exactly the type of questions, and I think the overall approach is not to look at an animal study and figure out what you can derive from it, but rather to be precise in your questions and figure out the right way to address them. You know, to the extent that you are concerned about some type of metabolism or skin enzyme, I don't think the answer to that is run it [a two-generation repro study]. You know, I think the answer to that is look at whether the material is, in fact, metabolized. So I think there's going to be a change, not only in the approach but in the fundamental way we address our questions.

DR. BOYER: And just to go back to a topic that we were discussing earlier, you know, a lot of funding, a lot of effort has gone into developing in vitro methodologies, high throughput test systems, and so forth, is geared towards supporting these alternative approaches, which is a very, very noval -- a very novel approach to this.

And, in fact, you know, the idea that we can use the toxicological data that's been accumulated over the past several decades from in vitro tests, from animals, to support that kind of analysis, I think has pretty much been debunked.

And so now the approach [is to] develop tests that are going to generate the data that can be very useful in supporting those kinds of [alternative] approaches.

DR. HILL: Yes. Having been immersed in the computational chemistry world long enough just to be dangerous, what they are looking for the most is data to validate the computational models. You have to have that. If you have a computational model with no experimental validation, it's worthless.

DR. BOYER: Right.

DR. HILL: The next best thing to worthless. That doesn't mean it won't get published in the literature, but it has no value until you can do some validation. And best-case scenario is humans, and where we have these accidental exposures so we know what the human toxicology looks like, you know. It's not the way you want it to come down, but that's the best kind of data for validating those kinds of models, honestly.

DR. MARKS: Okay. So I'm not exactly sure how I'm going to proceed tomorrow morning. Whether I'm going to make a motion to close this reopened report or whether I'm going to put up as a discussion and then be presenting the other option, as to keep it reopened with the intent of moving forward with PEG-2 insufficient, and the rest safe and reviewing add-ons.

Tom and Ron, is there -- are you leaning either way at this point. Ron Shank, before I talk to him, I'll probably call him later on today; it sounds like he would favor closing this reopened report; but do you have any strong feelings, or should we just let -- done?

DR. SLAGA: Well we don't -- We'll not be doing it, we just have to bring it up as a discussion tomorrow, right?

DR. MARKS: Yes. Well, we are going to make -- we'll have move forward tomorrow one way --.

DR. SLAGA: Making a recommendation for.

DR. MARKS: Yes. Is there any way – is there either one of those you prefer? Close the reopen or use the option of PEG-2 insufficient, and the rest safe for reviewing add-ons?

DR. SLAGA: I could go with that.

DR. MARKS: Okay.

DR. BERGFELD: I think that's probably the way it ought to go.

DR. MARKS: Yes. Okay.

DR. SLAGA: Because, how long have we been looking at this?

DR. MARKS: Well, since 1999. That's when the original report was. So, okay; what we'll do is move that we proceed forward with PEG insufficient, the rest safe. And then, yes, if you have any specific add-ons, if you can you can look at that, Ron Hill. Include the tallow amines, I heard, was a question mark.

DR. HILL: No. I think you would include them for the framework.

DR. MARKS: The framework. Okay.

DR. HILL: For the new -- for the purposes of data analysis. But that wouldn't be the same as adding them in. How would that be looked at in terms of -- we wouldn't be reviewing the safety those, right? We are just using that information.

DR. BOYER: I guess that could be one approach.

DR. MARKS: I think it would be possible if you get a succinct list now that would be included in this; because I don't see PEG-4 in here; I see PEG-2, 3, 5. Was PEG-4 in there?

DR. BOYER: It isn't.

DR. MARKS: Okay. Because the original assessment was PEG-4 was not.

DR. BOYER: Mm-hmm. That's right.

DR. MARKS: So you would have difficulty, I get the sense, Ron Hill, of PEG-2, 3, 4.

DR. HILL: Yes. Unless we have PEG-2 data to use -- to read across, which to some extent we do, but.

DR. SLAGA: Right. That's why we picked 2, so that we could go up the ladder, so to speak.

DR. ANSELL: And I think -- So precisely we are going to suggest reopening, and then redefine the family consistent with the data?

DR. MARKS: No.

DR. ANSELL: No?

DR. MARKS: We are -- it's already reopened.

DR. ANSELL: Okay.

DR. MARKS: So what I'm going to move tomorrow is that we -- probably something in effect, issue a tentative report that PEG-2, 3, 4 is insufficient. The rest are safe. We've got to do add-ons and that we support the SAR framework. So it would be moving forward to a tentative amended report is how I would see it.

DR. BERGFELD: Can you look on Page 129 and see a list that's there?

DR. MARKS: 129?

DR. BERGFELD: They asked if those were acceptable add-ons, and there are several PEG-2s (inaudible).

DR. MARKS: I've got the top part. Yes. And 2, but that was just say part of the list. So it would be nice to see everything.

DR. BERGFELD: It was larger than that?

DR. BOYER: Excuse?

DR. BERGFELD: Is the list larger than the one you have on Page 129?

DR. BOYER: On 129? Well there are -- the ones that are identified as PEG-2 are specifically the PEG-2 analog or add-on. But the ones where it's not specified as PEG-2 those -- each one of those represents a spectrum.

DR. BERGFELD: A spectrum.

DR. BOYER: Right.

DR. BERGFELD: Okay.

DR. BOYER: That could include --.

DR. BERGFELD: So you'd be taking that then PEG- 2s, yes.

DR. BOYER: That often includes the PEG-2.

DR. MARKS: Yes. I think, obviously we are going to -- I don't know if we -- unless we can perhaps identify the specific ingredients tomorrow, maybe it wouldn't move as a tentative amended report, it would still be an amended report in progress, so to speak. And the next time you would present a draft tentative amended report.

DR. ANSELL: Yes. We would like to see the actual ingredients listed. I think we are actually probably more conservative than that. We are drawing the line at about 15.

DR. MARKS: Yes. I have the HRIPT, PEG-15. Yes.

DR. ANSELL: Yes. And then maybe less than 15 for rinse off; but we are not sure that -- We want some further clarity on some of the tallow amines as to whether, you know, for the structure. We'd like to have another chance to look at the family outside of a philosophical discussion but relatively, maybe a more iterative list.

DR. BOYER: Yes. The entire list, is on Page 84, really, it's the chemistry section. It's not simply a list. But if you go down through the chemistry section you'll see all of the ingredients that have been proposed.

DR. MARKS: Well, I can't imagine -- Tom and Ron, will it feel difficult making it cut off at PEG-15 at this point?

DR. HILL: No. That's okay.

DR. MARKS: So let me see. Move; still not say for PEG supporting, say, a framework. Option is to -- So Ivan you would give us -- the next step would be a draft tentative report. How does that sound? Does that sound reasonable, Ivan?

DR. BOYER: Sure.

DR. MARKS: Okay. Any other comments? I knew this was going to be fun.

DR. BERGFELD: I think you should recap what you've just done.

DR. MARKS: Okay. So tomorrow I'm going to -- the first part in discussing this SAR that our team still does not feel safe with this SAR read across for PEG-2 cocamine. However, we do support the SAR framework and it's a useful tool for toxicologic review. The option in discussing it that we felt most comfortable with is to have PEG-2 and possibly less than PEG-15 as insufficient in the amended report, and the rest safe. We've got to review add-ons again. We include the tallow amines. And that the next step for Ivan would be to present a draft tentative report for us to review.

DR. LORETZ: That would be draft tentative amended report.

DR. MARKS: Yes. I'm sorry. Yes. Thank you.

DR. ANSELL: Draft tentative amended.

DR. MARKS: Yes. And the idea they amended it is to move forward at least for safe -- for some of these ingredients, and insufficient for possibly anything less than PEG-15. Okay. Does that capture it?

SPEAKER: Mm-hmm.

DR. MARKS: That was a robust discussion.

SPEAKER: It's good.

DR. HILL: So what do we do about add-ons though? That's the -- I mean, I know -- I'm still a little fuzzy. We look at some that we would potentially add in upon reopening, or we would be looking to add them all in? Or add them all in and then reject as --.

DR. MARKS: Yes. I think as a draft report we have the option at that point. When it's all put together we can delete the add-ons we want, or we discuss the SAR that supports them.

DR. HILL: Okay.

DR. MARKS: But I think anything that has a PEG-2 in front of it is obviously not going to be sufficient.

DR. HILL: Well I think 5 -- I think and below, what concerned me, because --.

DR. MARKS: Yes. So you've got 5. I agreed with Jay when he picked 15. And I think we'll have the Science and Scientific Committee input also at that point.

DR. ANSELL: Yes. We were thinking below 15 rinse-off than with eliminating the 2 so, it's just where we would draw the lines.

DR. MARKS: The good thing is that we'd get another look at this and we really deep dive into the SAR (inaudible) here.

DR. ANSELL: Yes. If we could keep the framework discussions separate from the details of this report I think that would be helpful.

DR. MARKS: Yes.

DR. ANSELL: Because the decisions on these specific ingredients aren't based solely on a single computational model but all the data. And that is something that the Council feels very strongly in favor of.

DR. MARKS: Okay. Does that sound clear to you, Wilma?

DR. BERGFELD: It does. It does.

DR. MARKS: Okay. I want to put PEG-2 to 5 insufficient, since that's where you feel uncomfortable with up to 5 the whole way. Well, again, it will flesh out as we move forward. Okay, any other comments? Let me be sure that I saved all these comments. I'll have the (inaudible) on it tomorrow, where was it?

Monday, December 8, 2014

Dr. Belsito Team

DR. BELSITO: …So now I guess we go back to PEGs cocamine, which is in the admin document. I'm used to admin documents being quick to review. This was -- you should label it "admin not quick." (laughter) Not admin, add many minutes. (laughter).

PEGs cocamine. So I hit "bookmark" and that takes me down to -- so basically this all revolves around the fact that we've gone insufficient for the PEGs cocamine in the past and they're being used. And then they'll go on to a black list unless we do something about them. And so we reviewed limited data on PEGs cocamine and related data on PEGs and determined that the data for PEGs cocamine in 1999 were not sufficient and that we wanted physical and chemical properties, genotoxicity, dermal carcinogenicity, using NTP if the genotox in mammalian was positive. A 28-day dermal on PEG-2 cocamine. That was when we were still very concerned about the low molecular weight PEGs before we had actually done the PEG report, including PEG-2. And then dermal sensitization for PEG-2 cocamine.

They were skin irritants at a time when we used to try and set concentration of limits for irritants and didn't realize it all depended upon how they were formulated and we really couldn't do that and came up with a boiler plate of when formulated to be non-irritating. So I think that issue sort of goes away, at least the irritation issue.

And ocular irritancy, PEG-15 cocamine has some Ames, negative Ames, the ethylene glycol metabolites and reproductive toxicity, we've taken care of with an ethylene glycol boiler plate, dioxanes and ethylene oxide impurities, we've always dealt with in discussion. Industry has submitted basically a number of structural activity relationship models as to how to look at the low molecular weight, mid molecular weight and higher molecular

weight PEG cocamines and identify structures of interest that we can use as comparators for read across. And all of that is in this background material that is in this tab.

And Ivan has developed a strategy memorandum looking at that. The question is, we still don't have a lot of data on PEGs cocamine. I think it's PEGs-15 cocamine that we got a little bit of data on. But having wrestled with a lot of issues that kept us insufficient for the PEGs cocamine, like irritation, et cetera, ethylene glycol, low molecular weight PEGs in that -- in previous reports, are we now comfortable going forward and issuing a safe as used? Because -- or are we still insufficient?

DR. BOYER: I guess we are asking the panel to really comment on two parts of this exercise. One is of course what you want to decide for the PEGs cocamine as an ingredient group. But also on the framework, we'd like to have your comments on how well or how not so well that framework does in terms of pulling everything together. Pulling information from diverse. sources to try to identify analogs based on a number of -- information in a number of areas, including chemical reactivity, metabolism, chemical properties and so forth.

So we would like some direction from the panel about -- well, first, where we think -- where you think we might take this particular approach, which is -- this is really just the first exercise that we're presenting to the panel. It's been presented before in Dr. Karen Blackburn's presentation at the SAR workshop. It's presented in your package in a little bit more detail. It incorporates information that we got from the submissions from the SSC. And hopefully it's presented in a manner that can be absorbed and evaluated by the panel fairly easily.

DR. BELSITO: I mean, I think the algorithms were very good, yes, no, if no, da, da, da. As Dan will say, it's the same thing we're going through with the fragrance materials, having to create algorithms as to when is it appropriate to read across, and how do you do that? So I thought it was very well laid out. And again, I don't have the expertise that Dan has in all these metabolic pathways. But I was very comfortable with what was presented. So comfortable that I thought we could go safe as used when formulated to be non-irritating, and the major question was whether we add in the PEGs oleamine, tallow amine, hydrogenated tallow amine, soy amine, rapeseed amine, steramine, lauramine and palmitamine.

DR. LIEBLER: So I thought to answer that latter question was yes for all of those. So you've had a couple of bullet questions. One was that, and the other one was --.

DR. SNYDER: Page 129.

DR. LIEBLER: All the ingredients were okay. And then should the PEG-2 ingredients be included? I said yes. Should tallow amine, phosphate be included among the analogs? I said it's an interesting question, but it really raises a larger issue of what to do with the "acceptable with interpretation." Or not -- acceptable -- is it acceptable I guess..

So let me make a couple of comments on the overall framework and the approach. You saw -- I think the strengths are that this is a systematic approach to something that we typically handle in a pretty ad hoc way. The idea of read across. I think from my time on the RIFM panel, I think RIFM's a little bit ahead of the game in terms of really trying to come up with a systematic approach for doing this. But I think it is time to do this, and this is a big step forward by itself.

I like the idea of trying to separate analogs into potentially quantifiable groups. The ones that are clearly suitable. The ones that are suitable with interpretation and the ones that are suitable with pre-condition. But I think the weakness of this approach as it is, is that it's on its way to being a good approach, but it's not a good approach yet. Specifically with these latter two categories, because suitable with interpretation and suitable with pre-condition, it seems to me that the basis for including an analog in one of those two groups is pretty arbitrary.

It's still a matter of judgment that you put them in there. And then there is no -- so being a matter of judgment, in a way, it kind of undercuts the systematic nature of trying to do this by the rules. Because if you don't have some kind of a quantitative or some kind of metric basis for deciding what to include or what not to include, you're kind of stuck. And in fact the categories about, of suitable with interpretation and suitable with pre-condition, in a way kind of collapse together if you don't clearly enough define what separates them.

DR. BELSITO: We've done that with RIFM too 'cause if you remember, with Cramer classification, if different predictive models gave different results, it ends up going to expert judgment.

DR. LIEBLER: Oh yeah, right. But we don't have -- I mean, it's true, that's a weakness there too. But it's still a weakness, okay. It's a weakness of trying to develop a systematic. approach. And I think this is one of the issues that needs to be solved. Otherwise what we're doing is, at least -- the good thing is we're systematically laying out the information and considering it.

But when it comes to critical steps of deciding which analogs to make decisions on, such as using the alkyl phosphate analog in this case, I didn't see any quantitative basis for a decision to use that or not to use it. It simply got rolled into the pile of read across and used. You do lay out a case for this could be in a separate category where some pre-conditions need to be met. Obviously it's the assumption that it's being metabolized in vivo to the unphosphorylated form, which then becomes the analog that would be suitable.

But there's no -- that's just a sort of a plausible scenario that isn't verified in any way.

DR. BOYER: So in other words, if there were data presented that showed that in fact the phosphate is metabolized, that's what you would be looking for. That's what you mean by --.

DR. LIEBLER: Substantially metabolized too. I mean, again -- and that's -- I'm doing it to myself. What do you mean by substantially? Greater than 50 percent? Greater than 75 percent, et cetera? But I think without having some quantitative basis for saying go, no go with using these or not using these in the read across, right now you basically have these categories, which are nice. But you don't have any qualifications that allows you to reach into that category and use that thing, that analog for read across. You simply are using this to separate the analogs into categories. But there still appear to be no restrictions on whether you actually use them.

DR. BOYER: Well, it's actually a two step process. And what you're referring to now I think is the very first step in the process, when [the medicinal] chemist goes in and makes some professional judgment, helped by whatever data is available, whatever data that they can look at. And they come up with basically a list of candidate analogs and they categorize them, and they present that to the toxicologist who then is tasked with looking at the information that's available on the structures of interest and the -- all of the candidate analogs and determining whether or not -- looking at the whole picture, all of the information that's available for all of these structures, the toxicological information, the chemical information, the chemical reactivity information and so forth.

Whatever information might be out there by way of metabolism, whatever QSAR models might be brought into play to help predict what the metabolites might be and so forth. So just looking at the whole picture and seeing whether or not that information is concordant, whether there's consistency there.

DR. LIEBLER: You're doing that after the medicinal chemist in your scenario said -- gave that compound their blessing. And then that compound and all the data associated with that compound go into consideration now, right?

DR. BOYER: Right, although it's more of an iterative process. So the toxicologist will go back to the medicinal chemists and ask them questions to clarify the selections. It's not a one --.

DR. LIEBLER: Okay, so even if it's iterative, the first gateway decisions from the medicinal chemist in a way is a subjective decision.

DR. BOYER: Right now it really looks like a subjective decision because we haven't been presented with, as you say, the background data. Now we've been given more or less a qualitative statement or qualitative statements as to why the specific analogs would be chosen, why they'd be categorized as they were.

I think the hope is that there is that background, that there is that information that we simply don't have at the moment.

DR. LIEBLER: So I appreciate the challenge here, and I'm pointing it out 'cause that's what I'm expected to do here. But I think the thing that's missing is, this whole process has some aspects that are very nicely systematic. And then they've still got these decision points that end up being what we would call expert judgment. And that's a -- it's really a kind of a weakness if you're going to have a truly systematic approach to identifying and qualifying analogs for read across. And I'm not saying it's an oversight on your part. It's the core problem in this field right now, is having a way to deal with that, other than just having somebody give a compound their blessing or not.

So one thing that is starting to appear, I mean, in our most recent discussions on RIFM panel is the use of some similarity scoring algorithms for the structures to quality them for inclusion, like the so-called Tanimoto similarity score. You're probably familiar with that. Which I was only -- only recently heard about actually. But I mean, I think that some -- the thing about that that's good is, that actually it may be imperfect, but it's an attempt to introduce some quantitative basis for the decision.

And I think whatever the future iteration of this is, we should try and put some quantitative basis into the decision making process for these key decisions. They can be appealable. If the quantitative algorithm doesn't or does qualify a compound that -- whether it's clearly an error made because of the limitation of the current version of the algorithm or algorithms that are used. But I think incorporating some kind of quantitative measures or metrics into the process should be made a priority, even if it's imperfect.

There's always a place for expert judgment in trying to deal with the limits of our software and algorithms and so forth. But to make the key steps still be opinion essentially, or subjective, is a weakness of the approach. And that's just my main comment.

DR. BOYER: Thank you. By the way, I know of at least one very good paper that discusses Tanimoto scores and other scores like it and does a very good critique. I would probably like to send that to you for your comment, if you haven't already seen it.

DR. LIEBLER: Sure.

DR. KLAASEN: Please send it to me also.

DR. LIEBLER: The whole panel should probably see it.

DR. KLAASEN: Yeah, I would like to second a lot of what was just said, and I've always taught students over and over and over, if you can't quantify it, it's not science. And that's kind of where we're at here. And yes/no is not quantitative either. So that's -- if we're going to pretend that it's science, truly science and not having some opinions involved in the whole process, then everything has to be quantifiable.

And the thing that always scares me about these -- I know we have to do read across and all of that. But the thing that always scares me is if you look at some simple alcohols, like propanol, isopropanol, ethanol and methanol, kind of the same, except methanol you go blind. And so I don't think it's only the algorithms that aren't where they need to be. The data to put in the algorithms is probably an even greater problem. And these are tough questions, and it also depends what the sorts of processes are really trying to do.

So if you're with the EPA, for example, what you're trying to do is, how do you -- of these five million chemicals or whatever that are out there in the environment, which ones look the most dangerous? That's quite a different question than what we're probably asking here, is that we have these chemicals, we're using them, and is what EPA doing over there appropriate to here?

Now my personal opinion, which isn't -- I shouldn't say as a toxicologist, but when you get to this age, maybe you're a little more honest. What is the number one problem in all of this? Is we look at -- we try to look at what the adverse effects are. We try to look at the dose response. Then we look at exposure. What we all should be doing, number one, is looking at exposure first.

I mean, if the exposure to some chemical is less toxic than anything has ever been in the entire toxicology database, why should we spend a lot of time on it? Instead of the other way around. That's especially true for EPA.

They got these five million compounds or whatever it is, but how many of them are people exposed to more than one picogram per lifetime? And is there any chemical in the world that you're exposed to at one picogram per lifetime that you should be concerned about? I doubt it. So that's my philosophy for today. For this afternoon. Until we go to the bar. (laughter).

DR. BELSITO: We're not allowed to discuss business at the bar.

DR. SADRIEH: I just want to add that the EPA also look at exposure to the environment as well and to ecological species as well. So it's not just human exposure that's evaluated. So even if human exposure may not be that high, one has to consider potentially exposure to other species which might be of concern.

DR. KLAASEN: I agree.

DR. BOYER: Yes, and we also have the threshold of [toxicological] concern approach that attempts at least to deal with that second issue that you brought up.

DR. KLAASEN: I would like to see that emphasized a little bit more. So what is the -- what is -- as a question, what is the most toxic chemical that's ever been put on the skin that produces toxicity other than burning? I don't have the slightest idea. But if you knew what that number was and we're putting less than that on a -- in a cosmetic, do you need all of this data? Just a kind of a flip way of looking at things.

DR. BOYER: And one of the central issues that we're trying to deal with is, we have data on many chemicals. We know the answers to many questions for quite a large number of chemicals. But there many others out there, many more, for which we don't have any data whatsoever. We don't have any test data. And I think that this framework and some of the research programs that EPA has undertaken and so forth, that it's trying to deal with that issue. In other words, rather than using costly whole animal studies, that in some instances [are questionable as] well, as to relevancy in themselves to human exposures, how do we develop in vitro assays in particular using human tissues, human cells, human test systems and so on to actually produce data that can be used to support QSAR or other types of alternative analyses?

DR. KLAASEN: I would agree that there is a tremendous amount of work going into this area, and it would be important, once we get the data, and if it's verifiable. I mean, I think using it for prime time, that is for really making decisions, there's not too many well established toxicologists that say that you should do it. It's still an experiment. It's not anything is defined..

I mean, first of all, in most of those tissue cultures, okay, so every -- if the government thought we'd be smart, we would use human tissues. Well, what's human tissues? They're a bunch of dead cells, they're not normal. And they're cell lines, and they don't tell you much. In fact there are great publications out recently, if you take an area that I'm interested in, is that if you're interested in various cancer cell lines, and look at the gene expression of those cell lines, now take those same cancers from humans. Take out those cells and run a gene array. You see opposite genes that turn on, 100 percent opposite. And this is done by the number two guy at NIH.

I mean, so what do our in vitro tests tell us? I don't know. I'd rather see a mouse study than an in vitro test at this time in history. Twenty years from now it might be different. But I think we need to be a little cautious of -- just because somebody's doing something as an experiment, to say that it's ready for prime time, we've got to be careful. That's all.

DR. LIEBLER: So I'd like to just suggest that when we talk about this tomorrow, the main question I'd like to bring forward is, where do we really want to go with this? Do you want to use this routinely in all safety assessments for read across? Do you want to use this for tricky cases? How much extra -- I mean, doing -- carrying out the analysis according to the framework you describe, how much extra work is that? Does that become a bottleneck? Let's try and ask some practical, useful questions for how this applies to our safety assessments. And you don't need to respond to all that here, but that's a discussion I'd like to have tomorrow with the full panel.

DR. BOYER: Okay, I think that would be great. What we would like to do is basically develop a little side project at the very least, where we might take some additional case studies and apply this particular approach using whatever information we can dig up to fill data gaps.

DR. LIEBLER: I fully support that.

DR. SADRIEH: I just want to add that I don't think that in vitro tests are intended to be predictive of what happens in the human. At least my understanding of in vitro studies are to understand specific mechanisms. You understand individual. You look at individual mechanisms and each assay is to tell you that individual mechanism that you're looking for. And it's not intended to be a surrogate for a human. I don't think that animal studies are oftentimes good predictors of what happens in the human either.

So I think while animal, whole animal studies are better in certain situations than in a single in vitro study, I just wanted to say that the same problems that might arise from extrapolating from an animal to a human, yes, you can have from in vitro to an animal and then from an in vitro to a human. But you should never try to extrapolate from an in vitro to a human or to an animal. You're specifically studying a mechanism, a single mechanism. That's the only thing. That's why you would need multiple in vitro assays to try and look at even a pathway that involves a number of different steps. So I just wanted to caution everyone that I don't think that in vitro is going to be bad per se, because it depends on how one looks at the in vitro studies.

DR. KLAASEN: I would agree with you 100 percent. What I am concerned about is going directly from in vitro -- using the in vitro data for risk assessment. Okay, and that's what we're kind of talking about here, is using the in vitro studies for risk assessment. Yes, in vitro studies can be very useful, but it has to be very specific often mechanistic wise. But to use it for risk assessment, is dangerous.

DR. BELSITO: I would agree.

DR. SADRIEH: It also depends on how much you know. I mean, if you know exposure, if you know a lot of other information, it might still be useful..

DR. KLAASEN: One has to use all the information that you have. I agree with that. And it can be very useful. But you have to be cautious as well. That's the word that I'd put.

DR. BELSITO: I mean, I would agree. But again, increasingly, given the restrictions coming out of Europe for animal testing for an ingredient that would be purely cosmetic, we're going to have to get used to interpreting in vitro data and deciding how to assimilate it into our safety assessments.

I mean, I thought the strategy was good. Again, I thought in terms of the PEGs cocamine and the other potential add-ons, we could go ahead and add them in. And to me, the issue was really just when formulated to not be irritating, I guess the one thing that sort of blew my mind was that PEG-2 rapeseedamine had 255 reported uses and not a single concentration to give us any guide. I mean, I just put, how is this possible that VCRP has 255 uses and not a single company we queried said they used it?

And particularly since PEG-2 seemed to be one of the hang ups we had. You're having a large number of uses on a PEG that we're concerned about and no concentration of use. It just -- I mean, I know Carol you tried. So I'm just -- this is a rhetorical question. I don't understand how that happened.

And then when we listed the ingredients on table four, was there a reason we went out of numerical order for the PEG cocamines? I mean, this is again, just my being anal compulsive, but --.

DR. BOYER: That was taken from the original report.

DR. BELSITO: I see. This is page 95. And if we are going to go ahead, and I haven't heard anything from my panel about my team I should say, with the safe as used, we need the respiratory boiler plate. We need the idea -- particularly with the, I guess it was the -- was it the tallow where the unsaturated fatty acids can form epoxides?

We would need to say something. about that. The more the unsaturation, the greater the ability to form epoxides. So we need to do something about that in the discussion.

And I would agree with the sensitization on the -- this is page 128, when we're looking at the PEGs-4 cocamine. I mean, as has been shown for linalool and limonene, it's the auto oxidization products that are the sensitizers. So this is a weak sensitizer and probably based off of oxidation, hydro peroxide formation. So we would need to say something about that in the discussion. Should be formulated to minimize auto oxidization when dealing with the -- in particular the -- this was, again, I think tallow, right? (Inaudible) no, it's PEG-4 cocamine, but -- so anyway, that's where I was. I mean, I thought we're okay going safe as used when formulated to be non-irritating and in discussion, auto oxidization. Not likely to occur. And botanicals, since there are some plant derived metals in pesticides.

DR. SNYDER: I think we should deal with bullet points, number two. I think Dan (inaudible) partially did that on page 129. Is that what -- did you have the answer to those, about those add-on ingredients, PEG-2?

DR. BELSITO: It's actually one -- it's 129. So do the select analogs adequately cover the chemical space of this ingredient? I thought I was okay.

DR. SNYDER: I was actually -- I thought we already kind of addressed all of that and moved to this number two about the add-ons and then the PEG-2 and then the tallow.

DR. BELSITO: Well, Dan said he was fine with that. That was one of the questions I already asked him. Are you okay with that?

DR. LIEBLER: Yes.

DR. SNYDER: And then in that -- under that add-ons, then with the rapeseedamine, do you want to have -- do you want to ask for data on concentration?

DR. BELSITO: Yeah.

DR. SNYDER: I think if we have that many uses, we have no concentration data. That's kind of a guess.

DR. BELSITO: I don't know that we're going to get any more. So I guess it gets back to we expect the concentration to be used to be the same as --.

DR. EISENMANN: But you know, all the uses are hair dyes. So I suspect it's a similar -- there's PEG-2 oleamine in hair dyes that you have concentrations. So I expect that the concentration is similar there.

DR. BELSITO: Well, I mean, that's what I'm assuming. And we always say as used, so that we'd go back to looking at how other of these chemical groupings are used in hair dyes. I just -- it was a rhetorical question, 255 uses and not a single concentration reported from industry was sort of mind boggling to me.

DR. EISENMANN: I will ask, but I think at least in this case, I'm pretty sure it's a safe bet it's a similar concentration as the PEG-2 oleamine.

DR. BELSITO: Well, we can always put that in the discussion too. That we were -- we note that it had 255 uses. It was used in this group of cosmetic products, and we're assuming that the concentration level is similar to PEG-2 oleamine that is also used primarily in hair eyes or something to that effect, could go in the discussion. I just think it needs to be addressed because it just looks ridiculous to me.

DR. LIEBLER: So we're going to proceed with the report. Doesn't look like we have any land mines. We've pre-identified where the issues are, but nothing's insurmountable.

DR. BELSITO: Right.

DR. LIEBLER: Okay.

DR. BELSITO: Weak sensitizer, hydro peroxides, be careful in formulations that would produce those and we are concerned about an ingredient with a large number of uses without concentration range. But we're assuming that it's used in this type of product, as is PEG oleamine and it's used in the same concentrations and formulated to be non- irritating. And then I guess the other issue would be, do you want to put non-sensitizing? Or do you just want to put in the discussion about auto oxidization? 'Cause I think the sensitizing ingredients are the hydro peroxides. I mean, and it was a weak sensitizer PEG-4 cocamine. I don't care one way or the other.

DR. LIEBLER: I think we're getting ahead of ourselves. It's a pre-report, right.

DR. BELSITO: Yeah, no, but I mean, we can go out as a final if we decide what the conclusion is. But if we suddenly decide to change the conclusion, then we have to retract it. I mean, do we want to go out with a final, safe as used, non-irritating with that discussion about hydro peroxides? Or do what we did with cocamido propyl betaine or whatever one and say both non-irritating and non-sensitizing?

DR. GILL: I think this has to come back as a tentative report. I don't think it's gone out as a tentative.

DR. BELSITO: Right..

DR. LIEBLER: We can't go from a pre-report to a -- if this is a category of report --.

DR. BELSITO: No, it would go out as a tentative final. Could it not go out as a tentative final?

DR. GILL: Right, tentative.

DR. BELSITO: But then if we change the conclusion, then it has to go back out again as another tentative final. So my point is, is the conclusion just going to be non-irritating and with a discussion of hydro peroxides in the discussion? Or is it going to be non-irritating and non-sensitizing as we've done for some other ingredients? Now we did it for other ingredients because we couldn't come to a basic understanding of the concentration of, I think it was DMAP and cocamido propyl betaine. Or it was one of betane, sorry. (laughter).

DR. LIEBLER: You see I don't think we have those issues before us with these. So I'm not sure that we need to default to the non-sensitizing.

DR. BELSITO: Okay, but non-irritating I do think we need to default to.

DR. LIEBLER: Right.

DR. BELSITO: Okay, so when formulated to be non-irritating, okay. So that -- we're saying we're going out as a tentative final, including all the add-ons that were mentioned and seeing what Mark's team has to say to us.

DR. LIEBLER: Yeah, Jim's doing this one.

DR. BELSITO: Yeah, I know. So we get to sit back and see what he says and then critique it, hey.

DR. LIEBLER: Right.

Tuesday, December 9, 2014.

Full Panel

DR. MARKS: Okay, so in 1999 there was an insufficient conclusion for the PEG cocamines and related ingredients. In 2012, so two years ago, we reopened these ingredients. We asked for data needs and these have

been certainly met, and then there was SAR and QSAR to -- that industry provided to try and support the safety, particularly of PEG-2 cocamine, that was the sort of identified ingredient, which was insufficient.

So, we felt that we could move -- that there's still not -- our team did not feel it was safe with the SAR read across for PEG-2 cocamine, however we do support the SAR framework and its useful tool for toxicologic review, so the move would be PEG-2 to 5 -- Ron Hill, correct me if I have the wrong number of PEGs -- insufficient in less than PEG-15 rinse-offs as well as greater than PEG-15 would be safe. And we would do the add-ons, including the [tallow] amines. And we recommend Ivan go on to the next step, which would be a draft tentative amended report with that conclusion.

So, complicated. We spent a lot of time on this. We appreciate the --.

DR. BERGFELD: Belsito team, any comments?

DR. MARKS: -- SAR framework to try and arrive at safety for these lower molecular weight PEG cocamine, but we still felt that that was not sufficient.

DR. BELSITO: Well, we have already gone down that low with the PEGs. No, our team felt that we appreciated the identification of, you know, other structures of interest to be used to read across and felt that we could add in the PEGs cocamine and safe as used when formulated to be nonirritating, including down to PEG-2.

And in the discussion caveats, there were some issues about -- particularly the tallow ingredients being unsaturated and subject to auto oxidation leading to some weak sensitization, so in the discussion just talk a little bit not only about the botanical, the usual heavy metals and pesticides, but also that they should be formulated to minimize auto oxidization and production of potentially allergenic hydro peroxides.

DR. BERGFELD: Ron?

DR. HILL: While I agree with you that we have looked at PEGs down to PEG-2, the situation is very different here than, for example, PEG esters, because in this case we have the moieties directly attached to an amine moiety, which renders the whole situation extremely different.

And so, we have a hydroxyethylamine, and again we have to remember when we have PEG 2, that that's going to mean that some of the nitrogen moieties won't be tertiary anymore, they will secondary amine or possibly even primary, but the main thing is, you know, only one hydroxyethyl or a hydroxyethyl oxyethyl moiety on one of the nitrogens and nothing for that third (inaudible), again, a secondary amine.

So, at the low molecular weight, because PEG-2 is an average and we have PEG-4 is an average, which means we can have 2 plus 2, but we can also have 1 plus 3 or even 0 plus 4 and the same with 5. We're in a regime where we've got a nitrogen there and, for example, if you were to sulfate or glucuronidate that terminal hydroxyl, which we don't know whether, one way or another, will happen, we can make the prediction, yeah, it might happen, it might not, we don't know. There's a possibility for cyclization, intra molecular cyclization, we could generate reactive intermediates that could result in sensitization, so there's a lot of possible chemistries here with PEG-2, 3, 4, up to 5, because they're averages, and we can have some residuals that won't be captured if we've just tried to read down using quantitative structure activity with very incomplete data about what humans are able to do in any potential route of exposure. And I think it would be a mistake -- we can cleanly deal with the ones that are PEG-15 and above and -- how far did we go down on rinse-off? Was it 10?

DR. MARKS: Five.

DR. HILL: Rive --.

DR. MARKS: But that actually could be covered with a nonirritating because obviously that's what we're doing with the rinse-off saying a rinse-off we can go lower than 15 because we would expect no reaction.

But I think the key is, those PEG-2 to 5, whether it's insufficient or -- you, obviously, Don, your team felt that the quantitative structural activity relationships (inaudible) --.

DR. BELSITO: [It was] convincing to us, at least that's what I felt. Dan, do you want to comment?

DR. Liebler: Oh, again, I took a little different approach to looking at these documents, particularly this document. I was more focused on the evaluation of the process of trying to apply a systematic approach to developing read-across, which has essentially been very idiosyncratic and haphazard and that's a major problem in the field, so my attention was not on whether or not I felt that the read-across that was arrived at justified the PEG-2 cocamine. That's an issue that we can address at end report and there still are potentially the opportunity to get data, which would be the best thing.

But I -- so, having said that, I think, you know, I know a number of Ron's concerns. I think that once again if we were to have that discussion today, we represent the typical yin and yang that we've had on these kinds of issues over the years. I'm obviously a little bit more favorably disposed to the question, but I think it's premature to make a judgment right now.

However, I would like to make a couple comments on the process as laid out by Ivan in his document. So, first of all, I think that the strengths are -- that it is a systematic approach and that's something that we need, and on the [RIFM] panel, we're going through the same thing. I think it's a very important, big step forward by itself.

Separating the analogues into different groups like suitable, suitable with interpretation, suitable with precondition, that's also useful in that not all analogues carry the same level of confidence in read-across.

I think this leads, though, directly to the weakness as it stands right now is that we don't have any kind of quantitative or metric-based way to say whether an analogue actually belongs in the suitable or suitable with interpretation or suitable with precondition bins. Again, it's a way of identifying possible analogues, but not in applying any level or measure of confidence that allows us to take the subjectivity or the expertness out of these steps. So, you know, perhaps the glass half empty way of characterizing this situation as it is right now is that we've laid out a better menu, but we still have the same kind of idiosyncratic way of choosing from the menu.

So, I would actually commend Ivan for the progress made and I suggest that we continue to pursue this approach. It may not solve our problem with this ingredient. It's in the long-term interest of the panel to have this approach driven forward and that I think what we need is quantitative aspects to the key decision making steps, and this is something that the RIFM panel is also working on and there's no point in reinventing the wheel. I hope that there's opportunity for continued dialogue beyond just the fact that Don and I are members of both panels.

So, those are my overall comments on this and I don't want to try and justify a decision on PEG cocamine at this point.

DR. BERGFELD: So, are you of the mind of removing it or calling it insufficient? I'm unclear of that platform that you're making.

DR. Liebler: Do you mean -- I'm sorry.

DR. BERGFELD: It's been proposed that PEG-2 to 5 be called insufficient.

DR. Liebler: I actually think it would be okay to call it insufficient. I would like to see data on PEG-2 because I think the read-across is -- you know, if you put a gun to my head and made me choose, I would go with the read across that we have, but I'd like to see data. So, if that's what we can get by putting out an insufficient that would be best.

DR. BERGFELD: Ron?

DR. HILL: I made the comment yesterday I wanted to be clear and firm that I was comfortable with the framework and approach, just that I wanted to be -- make sure that everybody was aware of that computational predictions in

the absence of data that can be used to validate those predictions for a particular class of chemicals is dangerous at best, insane at worst, so there needs to be -- and so a prime example came up, you know, the computation was done on one structure with PEGs 4, which is incorrect because PEGs 4 is not one compound, so that's a prime example where you need to, first of all, know what substance you're talking about and make sure the whole range of what's in that substance is covered and there is information to that effect.

And then, again, we had an extensive discussion about the fact that animals are not humans, and so validating with animal data, you could do that, you can validate with animal data but then what you know about is the mouse or the rat or you know about the humanized mouse or whatever it is that the animal is. So, that might be useful in terms of working on computational models but not necessarily valid when extending it to the humans except in selected cases.

So, in all computations you need to know what the boundary conditions are, you need to know what assumptions went into the computational model, and we need expertise that isn't on this panel, at least speaking for myself, in some cases about what exactly these black boxes are doing in a way that makes good sense.

But, in particular, when you make a computation on a substance, let's make sure that it's represented with the material we're talking about, so with PEG-2, PEG-4, PEG-5 and PEG-3, that's clearly not the case and also we were not picking up unsaturation and side chains that can also exist in these materials based on their definitions, so we need to take that into account because some of the reactivity that was -- that came up is that we take an unsaturated side chain and then partially hydrogenate it, now we may have trans fatty acids in there that are not consistent with natural -- the materials that are drawn from natural sources, and that may or may not have any consequence, but we don't have any data on that, then we're extrapolating where it's not merited, and that's a problem.

DR. BELSITO: So, you're going insufficient below PEG-5.

DR. MARKS: So, I will change my motion based on your team's input and we'll see where we arrive at. I move that PEG-2 to 5 insufficient, the rest is safe when formulated to be nonirritating and then we'll modify it as we --.

DR. BELSITO: Data from PEG 2 to 5 are the same data we had originally requested --.

DR. MARKS: Yes.

DR. BERGFELD: Is that a second?

DR. MARKS: And I think it will be helpful to have Ron Shank's input on the SAR too because I did capture all his notes yesterday, read them verbatim, and I think it'll be more robust to have Ron comment also.

His take was he was not totally comfortable with -- he looked at it as a research tool maybe not quite as comfortable -- we'll hear him speak for himself at the next meeting.

DR. BERGFELD: Any other comments? [inaudible]? Tom? I'd like to call the question then. All those in favor of approving this conclusion? Thank you, unanimous.

So, we have come to the end of our agenda. I'm going to ask Lillian if there's anything in parting that she needs to say in a moment. Do you have anything else that you need to tell us about or any comments?

Dr. GILL: I don't. I really want to thank the panel though for that very good and thorough discussion on the PEGs cocamine. That was very important to us. Thank you.

Safety Assessment of PEGs Cocamine and Related Ingredients as Used in Cosmetics

Status:	Draft Final Amended Report
Release Date:	May 22, 2015
Panel Date:	June 15-16, 2015

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ABSTRACT

The CIR Expert Panel assessed the safety of 47 PEGs cocamine and related ingredients, which are reported to function mostly as surfactants and antistatic agents. The Panel reviewed the relevant data and a systematic structure-activity relationship- (SAR-) based read-across assessment of these ingredients. The irritation potential of these ingredients is consistent with the surface-active properties that are characteristic of surfactants. The Panel concluded that the PEGs cocamine and related ingredients were safe as ingredients in cosmetic formulations in the current practices of use and concentration when formulated to be non-irritating. This conclusion supersedes the 1999 conclusion issued on six PEGs cocamine ingredients.

INTRODUCTION

This is a safety assessment of PEGs cocamine and related ingredients based on the relevant published scientific literature and unpublished reports. The PEGs cocamine ingredients reviewed in this report include:

PEG-2 cocamine
PEG-3 cocamine
PEG-4 cocamine
PEG-5 cocamine
PEG-8 cocamine
PEG-10 cocamine
PEG-12 cocamine
PEG-15 cocamine
PEG-20 cocamine
PEG-2 hydrogenated tallow amine
PEG-5 hydrogenated tallow amine
PEG-8 hydrogenated tallow amine
PEG-10 hydrogenated tallow amine
PEG-15 hydrogenated tallow amine
PEG-20 hydrogenated tallow amine
PEG-30 hydrogenated tallow amine
PEG-40 hydrogenated tallow amine
PEG-50 hydrogenated tallow amine
PEG-2 lauramine
PEG-2 oleamine
PEG-5 oleamine
PEG-6 oleamine
PEG-10 oleamine
PEG-15 oleamine
PEG-20 oleamine
PEG-25 oleamine
PEG-30 oleamine
PEG-12 palmitamine
PEG-2 rapseedamine
PEG-2 soyamine
PEG-5 soyamine
PEG-8 soyamine
PEG-10 soyamine
PEG-15 soyamine
PEG-2 stearamine
PEG-5 stearamine
PEG-10 stearamine
PEG-15 stearamine
PEG-50 stearamine
PEG-2 tallow amine
PEG-7 tallow amine
PEG-11 tallow amine
PEG-15 tallow amine
PEG-20 tallow amine
PEG-22 tallow amine
PEG-25 tallow amine
PEG-30 tallow amine

These ingredients include derivatives of the fatty acids of coconut oil, lauramine, oleic acid, palmitamine, rapeseedamine, soy acid, tallow, hydrogenated tallow and stearyl amine, as detailed in Table 1.

Most of the PEGs cocamine and related ingredients are reported to function as surfactants (eg, emulsifying, solubilizing, cleansing agents or foam boosters) or antistatic agents.[1] PEG-22 tallow amine and PEG-30 tallow amine are reported to function as hair conditioning agents.

This safety assessment includes a re-review of several of the ingredients addressed in a previous report. In 1999, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a final report on the safety assessment of PEG-2, -3, -5, -10, -15, and -20 cocamine.[2] The Panel concluded that the data were insufficient to support the safety of these ingredients for use in cosmetic products. Genotoxicity data were available from a single non-standard bacterial mutagenicity test in which PEG-15 cocamine was negative. Repeated-dose toxicity data were available from a single study in which 10% PEG-15 cocamine was applied to the shaved skin of rats 5 days per week for 6 weeks (30 applications), and no signs of systemic toxicity were found. However, no dermal sensitization data were available for these ingredients. Thus, the CIR Panel determined that the additional data needed included:

- Physical and chemical properties, including impurities (especially nitrosamines)
- Genotoxicity in a mammalian test system (if the results are positive then a dermal carcinogenesis study may be needed)

- 28-Day dermal toxicity using PEG-2 cocamine
- Dermal sensitization data on PEG-2 cocamine

Data specifically on PEG-2 cocamine were needed to demonstrate that relevant exposures to the ingredient with the lowest molecular weight in this group would not be toxic.[2]

The CIR Science and Support Committee (SSC) of the Personal Care Products Council (Council) contended that the gaps in genotoxicity and systemic toxicity data can be filled by applying a framework for identifying and evaluating analogs for read-across analyses.[3] The framework is based on the assessment of structure activity relationships (SARs), and enables the incorporation of information from the literature and predictive computational tools for physicochemical properties, chemical reactivity, metabolism and toxicity to identify suitable analogs and develop an overall weight-of-evidence safety assessment. The framework is described in detail in the published literature. The CIR SSC submitted two reports to the Panel, one in 2011[4] and another in 2012,[5] in which the framework was used to identify and evaluate analogs for a representative set of PEGs cocamine, and to read across from the data available for the analogs. The second CIR SSC submission was preceded by Dr. Karen Blackburn's presentation at the CIR Panel Workshop in March 2012, in which she explained the framework and illustrated how the framework could be used for read-across assessment of the PEGs cocamine and related ingredients.[6] The application of the framework to the PEGs cocamine ingredients (specifically the derivatives of coconut oil) was published in March 2015.[7]

The read-across analysis presented in the CIR SSC submissions,[4,5] Dr. Blackburn's presentation to the Panel,[6] and the March 2015 publication[7] indicates that these ingredients will not exhibit genotoxicity or systemic toxicity when used as intended in cosmetics. In addition, the CIR SSC's submissions and the March 2015 publication included computational analyses indicating that the PEGs cocamine, like the PEGs, are not dermal sensitizers.[4,5,7,8]

This safety assessment presents data and analyses from multiple sources, including the Council and the CIR SSC, to facilitate assessing the safety of the PEGs cocamine and related ingredients. The information submitted by the Council and the CIR SSC[4,5] included toxicological data from two US Environmental Protection Agency (EPA) High Production Volume (HPV) chemicals challenge reports[9,10] and three unpublished reports cited in one of the HPV reports.[11-13] CIR staff conducted a thorough search of the published scientific literature for information on the toxicity of all of the ingredients (original and proposed add-ons) and the analogs selected for read across in the CIR SSC submissions. The search yielded nothing of likely relevance for the assessment of these ingredients, except for the information presented in CIR's original safety assessment of PEG-2, -3, -5, -10, -15, and -20 cocamine. In this safety assessment, selected excerpts from the original safety assessment report are presented as *italicized text*. The excerpts are summaries of the information and issues that the Panel considered for the original assessment, and help to inform the present assessment as well.

Table 2 lists several previously-reviewed ingredients of potential relevance for this assessment, and presents the Panel's conclusion and highest reported maximum concentrations for each.

CHEMISTRY

Definition and Structure

The PEGs cocamine and related ingredients are polyethylene glycol (PEG) derivatives of the amines of fatty acids. The chemical structures of these ingredients conform to the following fundamental formula, where R represents alkyl groups derived from the fatty acids, and the x+y of the polyethylene glycol groups have average values equal to the number in the International Nomenclature Cosmetic Ingredient (INCI) name (Table 1).[1]

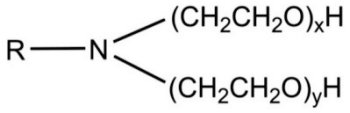


Figure 1. General chemical structure of PEGs cocamine and related ingredients

For example, PEG-4 cocamine is the polyethylene glycol derivative of cocamine, where R represents alkyl groups derived from the fatty acids of coconut oil and x+y has an average value of 4 (Table 1). Likewise, PEG-7 tallow amine is the polyethylene glycol derivative of tallow, where R represents alkyl groups derived from the fatty acids of tallow and x+y has an average value of 7.

Thus, each ingredient in this group is a mixture of substances with various lengths of the PEG moieties and various lengths and degrees of unsaturation of the alkyl fatty acid moieties (Table 1).[14]

The structure of PEG-2 cocamine and the other ingredients in this group with PEG-2 in the INCI name will have two *N*-hydroxyethyl groups, rather than two *N*-polyethoxyl groups, if x and y both equal 1, or one hydrogen atom and one *N*-polyethoxyl group, if x=0 and y=2. The Panel noted the possibility of similar structural variations for ingredients with PEG-3, -4, and -5 in the INCI name (Table 1).[14] The maximum reported secondary amine content of PEG-2, -3, -4, and -5 ingredients ranged from 0.5% to 0.7%, and the maximum primary and secondary amine content, combined, ranged from 1.2% to 5% (Table 3).

In coconut oil, saturated fatty acids with chain lengths of C12 (44% to 53%) predominate, and there were smaller fractions of unsaturated C16 (0% to 1%) and C18 (6% to 12%) chains (Table 4).[4] In tallow, by contrast, unsaturated fatty acids with chain lengths of C18 (39% to 59%) predominate, and there were substantial fractions of saturated C16 (20% to 37%) and C18 (14% to 21%) chains (Table 5).[4]

Unsaturated fatty acids with chain lengths of C18 predominate in rapeseed oil (>32% to >96%; Table 6) and in soybean oil (>40% to >60%) (Table 7).[15]

Chemical and Physical Properties

Supplier specifications and analytical data for some of the PEGs cocamine and related ingredients are presented in Table 3. These ingredients range in appearance from clear, yellow or amber viscous liquids to yellow pastes or soft solids, which generally reflects the lengths of the carbon chains, from short to long, of the chemical structures of these ingredients. They are soluble in water, as well as in acetone, isopropyl alcohol, and other organic solvents, and have very low vapor pressures at ambient temperatures. These ingredients can be prepared such that moisture does not exceed 1%.

Method of Manufacture

The PEG-n cocamine polymers are manufactured by condensing coconut acid with the ingredient's corresponding number of moles (n) of ethylene.[2]

PEGs are formed by condensing ethylene oxide and water, with the average number of moles of ethylene oxide polymerized indicated by the number in the name.[16]

Coconut acid is a mixture of fatty acids derived from coconut oil. Coconut oil is obtained by expression from the kernels of the seeds of Cocos nucifera. The primary constituents of coconut oil are trimyristin, trilaurin, tripalmitin, tristearin, and various other triglycerides. About 90% of the oil is saturated. The expressed material has a water content of coconut oil. The fatty material is isolated after hydrolysis of coconut oil and then distilled to form coconut acid.

The synthesis of ethoxylated fatty acids is essentially a two-step process.[6] The first step is illustrated in Figure 2.

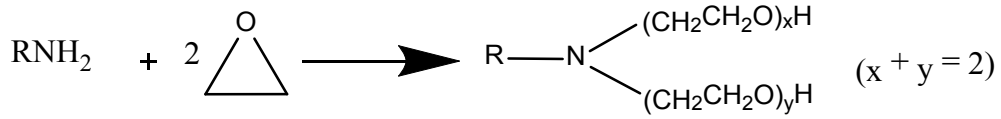


Figure 2. Ethoxylation of fatty amines, Step 1

This reaction proceeds until all primary and secondary amines are consumed, yielding the smallest members of this ingredient group, which the *International Cosmetic Ingredient Dictionary and Handbook* calls PEG-2s. The second step, which is illustrated in Figure 3, requires a catalyst.

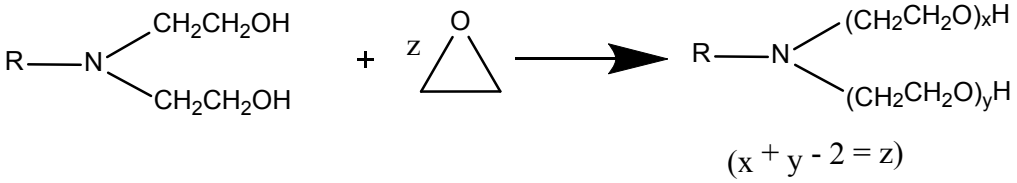


Figure 3. Ethoxylation of fatty amines, Step 2

The chain lengths of the PEG groups depend on the duration of the reaction, and these groups may not be symmetrical; typically, this reaction yields a range of PEG chain lengths.

Impurities/Constituents

Coconut oil is usually low in color bodies, pigments, phosphatides, gums, and other nonglyceride substances commonly found in larger quantities in other vegetable oils. It may contain free fatty acids, low concentrations of sterols, tocopherol, and squalene. The characteristic coconut flavor is due to the presence of approximately 150 ppm lactones that are present as a series of d-lactones with 6, 8, 10, 12, and 14 carbon atoms. Crude samples of coconut oil contain traces of polycyclic aromatic hydrocarbons, particularly when the copra is smoke-dried. A combination of activated charcoal treatment and steam vacuum deodorization are the common refining methods most likely to remove the hydrocarbons from the edible oils. Aflatoxin contamination of raw and dried copra have been reported. Improper drying, handling, and storage greatly increase the possibility of contamination by aflatoxins, secondary metabolites of the mold Aspergillus flavus, which grows on copra. Smoke drying of copra inhibited aflatoxin formation.[2]

The information available from some suppliers indicates that the tertiary amine content of the PEGs cocamine and related ingredients ranges from 95% to 98.7% minimum (Table 3), although one supplier indicates a maximum of 95% for PEG-2 cocamine (probably a minimum, because the same supplier indicates a maximum of 5% primary and secondary amines combined).[17] Primary amine content of PEG-2 tallow amine was 0.4% to 0.8%. The maximum content of primary and secondary amines, combined, ranged from 0.7% to 5% for these ingredients.

The PEGs cocamine and related ingredients, like the PEGs, may contain traces of 1,4-dioxane (which is a by-product of ethoxylation) and ethylene oxide as impurities;[2,16,18] 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 limit it in these ingredients before blending into cosmetic formulations. In addition, these ingredients are mixtures of tertiary alkyl amines that may also contain some secondary or primary amines. Thus, the formation of nitrosamines in formulation should be considered. The maximum concentration of nitrosamine was reported by a supplier to be 50 ppb in PEG-2 cocamine (Table 3).[19]

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated based on the expected use of these ingredients in cosmetics. The Panel evaluates data received from the Food and Drug Administration (FDA) and the cosmetics industry to determine the expected cosmetic use. The data received from the FDA are collected from manufacturers through the FDA's Voluntary Cosmetic Registration Program (VCRP), and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Council in response to a survey of the maximum reported use concentrations by category.

According to the 2015 VCRP survey data, PEG-2 rapeseedamine is reported to be used in 255 formulations, all of which are hair coloring (rinse-off) formulations, and PEG-2 oleamine is reported to be used in 254 formulations, all of which are hair coloring formulations (Table 8). All of the in-use ingredients were reported to be used in rinse-off products, except PEG-2 cocamine (in body and hand spray products; no use frequency reported), PEG-15 cocamine (in hair grooming aid, makeup base, and body and hand spray products; 4 reported uses), and PEG-2 oleamine (in a moisturizing product). The results of the concentration of use survey conducted by the Council in 2014 indicate that PEG-5 soyamine has the highest reported maximum concentration of use; it is used at up to 4% in hair coloring formulations. Similarly, the highest maximum use concentration of PEG-2 oleamine is 3.5%, also in hair coloring formulations. The highest maximum concentration of use reported for products resulting in leave-on dermal exposure is 3% PEG-15 cocamine in body and hand spray products.

The frequency of use totaled 107 for PEG-2 cocamine in 2015, compared to 15 in 1996, and 4 for PEG-15 cocamine in 2015, compared to 35 in 1996. The highest maximum use concentration for PEGs cocamine (length of ethoxy moieties not specified) was 20% in 1995,[2] compared to 3% PEG-15 cocamine and 3.5% PEG-2 oleamine in 2014[20,21]

Table 9 presents the current and historical product-formulation use data for ingredients included in the original PEGs cocamine report, and Table 8 presents the use data for the additional ingredients that are included in this safety assessment and that are reported to be used.

Table 10 lists the 37 PEGs-cocamine and related ingredients not indicated to be in use, based on the 2015 VCRP data and the results of the Council's 2014 concentration of use survey.

Some of the ingredients in use are reported to be used in body and hand sprays and could possibly be inhaled. For example, PEG-15 cocamine was reported to be used in body and hand sprays at a highest maximum concentration of 3%. 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.[22,23] 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.[24,25]

Non-Cosmetic

The predominant surfactant in a commercial herbicide formulation is a polyoxyethyleneamine tallow amine (aka polyoxyethyleneamine or POEA),[26,27] which is a mixture of polyethoxylated long-chain alkyl amines synthesized from animal-derived fatty acids.[27] The molecular size of POEA is not specified in the literature. The herbicide formulation contains 15% or more POEA, which has the same generic CAS# (61791-26-2) as several of the cosmetic ingredients addressed in this safety assessment (ie, PEGs tallow amine and PEGs hydrogenated tallow amine).[27] POEA is listed by US EPA as a pesticide inert ingredient.[28]

TOXICOKINETICS

PEG cocamine absorption and metabolism data were not available.[2] PEG absorption is related to whether the substance is a liquid or a solid. PEGs were readily absorbed through damaged skin. Oral and intravenous

studies on the PEGs indicated that these substances were excreted, unchanged, in the urine and feces. Ingested Coconut Oil was almost entirely absorbed.

Data on toxicokinetics of PEGs cocamine and related ingredients were not found in the published literature, nor were unpublished data provided.

TOXICOLOGICAL STUDIES

Acute Toxicity

The oral LD_{50} of PEG-15 cocamine in rats was 1.2 g/kg, and for PEG-2 cocamine, the LD_{50} ranged from 0.75 g/kg to 1.3 g/kg.[2] No systemic toxic effects occurred in rats following a 6-week dermal application study using 10% PEG-15 cocamine. PEGs have low oral and dermal toxicity; generally, the greater molecular weight PEGs appear to be less toxic than the lighter PEGs in oral studies. Coconut oil and hydrogenated coconut oil are relatively nontoxic by ingestion.

Oral

PEG-2 tallow amine

Sprague-Dawley rats (HC/CFY; n= 1/sex/dose) each received a single dose of PEG-2 tallow amine (95% purity) by gavage using an "up-and-down" method.[9] The test material was suspended in 1% methyl cellulose. Doses ranged from 1 to 5 g/kg for males and 0.8 to 5 g/kg for females. The rats were observed for 7 days after exposure. Piloerection and hunched posture were observed shortly after dosing in all treated animals, as well as pallor of the extremities, lethargy and abnormal gait in most of them. Ptosis, diarrhea and increased salivation were observed at doses ≥ 1.0 g/kg, and decreased respiratory rate at doses ≥ 1.26 g/kg. Necropsy revealed hemorrhage or congestion of the lungs in the majority of the rats that died before scheduled sacrifice, usually accompanied by pallor of the liver, kidneys and spleen. The female treated with 1.6 g/kg of the test substance exhibited congestion of the blood vessels of the stomach, and the female exposed to 5 g/kg exhibited congestion of the blood vessels of the intestines. No effects were found on necropsy of the rats that survived throughout the observation period. The LD_{50} was estimated to be 1.5 g/kg (95% confidence interval = 1.1 to 2.0 g/kg) for males and 1.2 g/kg (95% confidence interval = 0.9 to 1.6 g/kg) for females.

Ten Sprague-Dawley rats (n= 5/sex/dose) received a single 2 g/kg dose of PEG-2 tallow amine in peanut oil by gavage.[9] The rats were observed for 14 days after exposure. All of the rats exhibited hunched posture and piloerection 1 hour after treatment, but appeared normal 4 hours after treatment. None of the rats died before the scheduled sacrifice. No effects were found on necropsy. The LD_{50} was reported to be > 2000 mg/kg.

PEG-20 tallow amine

Groups of 10 albino Sprague-Dawley rats (n=5/sex/dose) received a single 0.547, 0.765, 0.918, or 1.071 g/kg dose of undiluted PEG-20 tallow amine by gavage.[9] The animals were examined for mortality and signs of toxicity 0.5, 2 and 4 hours after exposure, and then daily throughout the 14-day observation period. Many of the animals that died during the observation period exhibited diarrhea. Of the 8 rats in the 1.071 g/kg group that died during the observation period, one exhibited blood stains around the nose and mouth and another exhibited dark brown fluid in stomach. The LD_{50} was estimated to be 0.89 g/kg (95% confidence intervals = 0.78 to 1.01 g/kg) for males and females combined.

Groups of 10 albino Sprague-Dawley rats (n=5/sex/dose) received a single 0.16, 0.4, 1, 2.5 or 6.25 g/kg dose of undiluted PEG-20 tallow amine by gavage.[9] The animals were examined for mortality and signs of toxicity 0.5, 1, 2.5 and 4 hours after exposure, and then daily throughout the 14-day observation period. None of the rats of the 160 mg/kg group died during the observation period. Several animals in the 0.16 g/kg group showed mild signs of toxicity (piloerection, ataxia, decreased activity, discharge around the eyes, nose, and mouth, and diarrhea) during the first few days after exposure, but appeared normal within about 4 days. In addition to these signs, the animals of all of the other groups exhibited stained abdomen and anogenitals, emaciation, excess salivation, red crusty material around the nose, and decreased activity. Surviving animals of the 1 g/kg group also exhibited red crusty material on face, soft stools, decreased limb tone, prolapsed penis and hypothermia. Necropsy revealed a dose-dependent increase in the incidence of lesions associated with irritation, and fluid accumulation in the stomach and lower

gastrointestinal tract, as well as evidence of congestion in the lungs and thymus. The LD_{50} was estimated to be 0.63 g/kg of body weight (95% confidence intervals = 0.45 to 0.89 g/kg).

Groups of 10 albino Sprague-Dawley rats (n=5/sex/dose) received a single 0.69, 0.97, 1.17 or 1.36 g/kg dose of undiluted PEG-20 tallow amine (purity 96.7%) by gavage.[9] The animals were examined for mortality and signs of toxicity 0.5, 2 and 4 hours after exposure, and then daily throughout the 14-day observation period. Signs of toxicity during the first 9 days of the observation period included hypoactivity, diarrhea, soft stools, ataxia, urine or reddish-brown stained abdomen, decreased limb tone, hypersensitivity to touch, lacrimation, bradypnea, red stain around nose and eyes, high carriage, increased limb tone and tremors. All animals of the 0.69 g/kg group appeared to be normal by the second day of the observation period, as did the rats of the 0.97 g/kg group by day 6 and the 1.17 g/kg group by day 10. The single surviving animal of the 1.36 g/kg group appeared normal by day 8 of the observation period. The estimated LD_{50} was 1.15 g/kg (95% confidence limits = 1.04 to 1.26 g/kg) for males and females combined.

PEG-50 stearamine

A group of 10 albino Sprague-Dawley rats (n=5/sex) received a single 15 g/kg dose of 75% PEG-50 stearamine (purity 99%) suspended in distilled water by gavage.[9] The animals were examined for mortality and signs of toxicity 0.5, 2 and 4 hours after exposure, and then daily throughout the 14-day observation period. Signs of toxicity during the observation period included hypoactivity, diarrhea, ataxia, brown-stained anal region, red-stained nose and mouth, and death. All surviving animals appeared to be normal within five days after exposure. None of the gross findings observed at necropsy were considered to be treatment related. The reported LD_{50} was > 15.0 g/kg for males and females combined.

Dermal

PEG-20 tallow amine

New Zealand White rabbits (n=3/sex/dose) received a single 2 ml/kg application of undiluted liquid PEG-20 tallow amine on the clipped skin of the back.[9] The skin was abraded before the application of the test substance in two of the male and one of the female rabbits. The exposure sites were occluded with gauze bandages, dental dams, and tape for 24 hours after the application. Rabbits were observed twice daily for signs of dermal irritation for 14 days after removing the bandage and excess test substance. One female exhibited signs of respiratory congestion from day 3 through 14 of the observation period, and another female exhibited dehydration from day 10 through 14. Necropsy revealed that the lungs of a male rabbit were dark red with small, multifocal, raised areas. These lesions were considered to be attributable to a latent respiratory infection known to be common in this species, and were not considered to be treatment related. One lobe of the liver of a male rabbit exhibited pinpoint-size white foci, and a female had several, small tan areas throughout the liver. The etiology of the liver lesions is unknown. None of the animals died during the observation period, and the reported LD_{50} was > 2.0 ml/kg (male and female combined).

New Zealand White rabbits (n=3 [1 male and 2 females or 2 males and 1 female]/dose) received a single 2 ml/kg application of undiluted (Group 1) or 50% aqueous (Group II) PEG-20 tallow amine (purity 98%) on the clipped skin of the back.[9] The skin was abraded before the application of the test substance in two of the male and one of the female rabbits of each group. The exposure sites were occluded with gauze bandages, rubber dams, and Elastoplast tape for 24 hours after the application. Rabbits were observed 30 minutes and then daily for signs of dermal irritation for 14 days after removing the bandage and excess test substance. All of the animals survived through the 14-day observation period. None of the gross lesions observed on the lungs, liver and kidneys in 4 Group I and 2 Group II rabbits were considered to be treatment related. The reported LD_{50} was > 2 g/kg for males and females combined)

New Zealand White rabbits (n=3/sex/dose) received a single 2 ml/kg application of undiluted liquid PEG-20 tallow amine (purity 95%) on the clipped skin of the back.[9] The skin was abraded before the application of the test substance in one of the male and two of the female rabbits. The exposure sites were occluded with gauze bandages, dental dams, and Elastoplast tape for 24 hours after the application. Rabbits were observed 24 hours and then daily for signs of dermal irritation for 14 days after removing the bandage and excess test substance. Animals with intact exposure sites exhibited slight-to-marked erythema, atonia and coriaceousness, slight-to-moderate edema, desquamation and fissuring, eschar formation, exfoliation, subcutaneous hemorrhage and hyperthermia. Rabbits with abraded exposure sites exhibited moderate-to-marked erythema, slight-to-marked atonia and desquamation, slight-to-moderate edema, coriaceousness and fissuring, and subcutaneous hemorrhage and

hyperthermia. During the observation period, 60% of the animals died. The findings upon gross necropsy examination of the 6 surviving animals were not considered to be treatment related. The reported LD_{50} was < 2.0 mL/kg for males and females combined.

PEG-50 stearamine

A group of 6 New Zealand White rabbits (n=3/sex) received a single 2 ml/kg application of 75% w/v PEG-50 stearamine (purity 99%) in distilled water on the clipped skin of the back.[9] The skin was abraded before the application of the test substance in one of the male and two of the female rabbits. The exposure sites were occluded with gauze bandages, rubber dams, and Elastoplast tape for 24 hours after the application. Rabbits were observed 30 minutes and then daily for signs of dermal irritation for 14 days after removing the bandage and excess test substance. All animals survived and appeared normal throughout the study period, except for signs of dermal irritation. The signs included slight-to-moderate erythema and desquamation with slight fissuring and edema. The reported LD_{50} was > 1.5 g/kg (male and female combined) in this study.

Repeated Dose Toxicity

Oral

PEG-2 tallow amine

Groups of 25 young SPF Wistar adult male and female rats were fed PEG-2 tallow amine in the diet (*ad libitum*) at concentrations of 0, 170, 500 or 1500 ppm (about 15, 50 and 150 mg/kg/day) for 90 days.[4,5,9] An additional group of 10 male and 10 female rats was given a diet containing 4500 ppm of the test substance. Further, a group of 7 male and 7 female rats were fed the diet containing 4500 ppm PEG-2 tallow amine for up to 6 weeks, during which rats were selected from this group at intervals and sacrificed to determine the presence of sudanophilic material (indicating accumulation of the test substance) in the tissues. The test substance was dissolved in corn oil and mixed with the experimental diets. Body weights were recorded at the beginning of the treatment period and weekly thereafter. Hemoglobin concentrations, packed-cell volumes, white-cell counts and differential white-cell counts were measured before initiating treatment and then immediately before sacrificing the animals at the end of the 90-day treatment period. The liver, heart, lung, adrenals, kidneys and spleen were collected from randomly selected animals of each group and weighed, and organ/body weight ratios were calculated. Tissues and organs from the other rats were fixed and examined microscopically, including liver, kidney, spleen, heart, lung, adrenals, gonads, thymus, thyroid, pancreas, stomach, duodenum, jejunum, ileum, cecum, colon, salivary gland, mesenteric lymph nodes, spinal cord and brain (cerebrum, cerebellum and medulla). Rats fed diet containing 4500 ppm of the test substance lost hair and were lethargic throughout the study. Macroscopic examination at necropsy revealed yellow coloration of the stomach and bowel contents, and thickening and yellow coloration of the mucosa of the small intestines and the regional mesenteric nodes in rats of the 4500 ppm group. In this group, microscopic examination revealed engorgement of the *villi* and *lamina propria* of the small intestines with swollen foamy sudanophillic macrophages. The latter macrophages were observed occasionally, and to a lesser degree, in Peyer's patches and regional lymph nodes. The 1500 ppm group exhibited similar effects, although to a lesser degree than observed in the 4500 ppm group. Body weight gain was reduced in both the 1500 ppm group and the 4500 ppm group, which was attributed to the reduced palatability of the diets. No clinical effects were noted at any dietary concentration less than 4500 ppm, and no definite hematological abnormality, differences in organ weights, or abnormalities of the reproductive organs were found at any dietary concentration tested, including 4500 ppm. The reported no observed effect level (NOEL) was 500 ppm (about 50 mg/kg/day) and the lowest observed effect level (LOEL) was 1500 ppm in this study.

Four groups of 40 Crl:CD(SD)BR rats (20 males and 20 females) were fed diets, *ad libitum*, containing PEG-2 tallow amine at concentrations of 0, 0.001, 0.015 and 0.5% w/w for 28 days or until necropsy.[4,5,9,13,29] The test substance was added to the diets as 1% solutions in corn oil. All animals were examined at least once every day for overt toxicity or behavioral changes, individual body weights and group food consumption were recorded weekly, and hematology analyses and necropsy were performed on all rats. Weights of the adrenal glands, kidneys, lungs, testes, heart, liver and ovaries were measured at necropsy. Histopathological examinations were conducted for all animals in the control and high dose groups, and included examination of the reproductive organs. The jejunum and mesenteric lymph nodes of the animals in the mid-dose groups were examined. A high incidence of hair loss observed across all groups was not considered to be treatment related. Body weight gain was slightly

reduced in males and females exposed to 0.5% and in males exposed to 0.015% in the diet. Food consumption, hematology and organ weights were not different from controls. Histiocytosis (ie, aggregations of macrophages with foamy cytoplasm) in the jejunum and mesenteric lymph node in the 0.5% group was the only treatment-related histopathological finding in this study. There were no treatment-related effects on organ weights or in the histopathology of the reproductive organs in any of the exposed animals. The no observed adverse effect level (NOAEL) was estimated to be 0.015% (approximately 12 mg/kg/day), based on body-weight gain.

Groups of four male and female Beagle dogs were fed diets (*ad libitum*) containing PEG-2 tallow amine at concentrations corresponding to doses of 0, 13, 40 and 120 mg/kg/day for 90 days.[4,5,9] Body weights were recorded at the beginning of the treatment period and weekly thereafter. Hemoglobin concentrations, packed-cell volumes, white-cell counts and differential white-cell counts were measured before initiating treatment and immediately before sacrificing the animals at the end of the 90-day treatment period. Blood urea, serum alkaline phosphatase, liver function and urine analysis also were analyzed. The liver, heart, lung, adrenals, kidneys, spleen, thyroid, testes, epididymides, brain and pituitary glands were weighed when the animals were necropsied. Representative sections were collected for microscopic examination of the brain (cerebrum, cerebellum and medulla), spinal cord, pituitary, submaxillary gland, thyroid, thymus, heart, lung, aorta, stomach, duodenum, jejunum, ileum, colon, liver, spleen, kidney, bladder, adrenal, ovary and uterus or testes and epididymis, and sciatic nerve. The NOEL was reported to be 13 mg/kg/day, and the lowest observed effect level (LOEL) was 50 mg/kg/day. No other findings of this study were presented.

PEG-2 C13-C15 alkyl amine

PEG-2 C13-C15 alkyl amine was tested in rats in a 90-day oral repeated dose toxicity study.[10] PEG-2 C13-C15 alkyl amine is not identified as a cosmetic ingredient in the INCI Dictionary. However, like PEG-2 cocamine and related ingredients, PEG-2 C13-C15 alkyl amine (x+y=2) is a likely analog for these ingredients in a read-across assessment.

Groups of 40 Sprague-Dawley rats (20 males and 20 females) received 0, 15, 30 or 150 mg/kg/day PEG-2 C13-C15 alkyl amine by gavage for 90 days. The control groups were given deionized water.[10] There were no toxicologically significant treatment-related effects based on the assessment of clinical chemistry and organ weights, although urinalysis was not performed and the assessment of organ weights was described as limited. However, there were many clinical signs observed in the rats receiving 150 mg/kg/day of the test substance. These signs included wheezing and salivation (in all animals of this group and in some of the 30 mg/kg/day group), blood crust or red discharge from the nose, dyspnea, rhinorrhea, opaque eyes, redness, hunched posture, thin, urine stains, rough haircoat, desquamation and increased incidence of alopecia. Mortalities during the study included 4 rats in the 150 mg/kg/day group and 2 rats in the 30 mg/kg/day group. At 150 mg/kg/day, statistically significant deficits were observed in body weight and body weight gain (males and females) and food consumption (males). Ophthalmoscopic examination revealed posterior subcapsular cataracts at 30 mg/kg/day (males) and 150 mg/kg/day (males and females), and complete cataracts at 150 mg/kg/day (males and females). Histopathological examination showed inflammation in the lungs (150 mg/kg/day) and stomach (30 and 150 mg/kg/day), which was associated with statistically-significant elevations in mean platelet, white blood cell, segmented neutrophil, and lymphocyte counts in the 150 mg/kg/day group. The inflammation observed in the lungs was attributed to inadvertent aspiration. Desquamation and alteration of the mucosa of the non-glandular stomach was observed primarily in rats of the 150 mg/kg/day group, but also in some rats of the 30 mg/kg/day. Two females in the 150 mg/kg/day group exhibited suppurative inflammation of the glandular stomach. The reported NOAEL was 15 mg/kg/day, and the LOAEL was 30 mg/kg/day in this study.

PEG-15 tallow amine

In a 90-day oral toxicity study, PEG-15 tallow amine was administered in the diet *ad libitum* to three groups of 10 male and 10 female Sprague-Dawley rats.[10] The concentrations of the test substance in the test diets were approximately 500, 1500, or 4500 ppm (equivalent to about 33, 99, and 292 mg/kg/day for males, respectively, and 40, 123, and 357 mg/kg/day for females, respectively). The control group received the basal diet. Exposure to 1500 ppm or 4500 ppm PEG-15 tallow amine caused statistically-significant and toxicologically-significant effects. At 4500 ppm, clinical signs included soft stools (day 16 through day 92 of the study), decreased body weights (throughout the study) and decreased body weight gains. Food consumption was also reduced through most of the study. At 1500 ppm and 4500 ppm, microscopic examination revealed inflammatory changes in the digestive tract,

including hypertrophy and vacuolation of histiocytes in the *lamina propria* of the ileum and jejunum, sinus histiocytosis, and accumulation of macrophage aggregates in the cortex and medullary cords of the mesenteric lymph nodes. There were no treatment-related gross abnormalities, histopathological findings, or statistically-significant effects on body weight, body weight gain, food consumption, hematological and clinical chemistry parameters, or organ weights at 500 ppm. The NOAEL was 500 ppm (33 to 40 mg/kg/day) and the LOAEL was 1500 ppm (99 to 123 mg/kg/day) in this study.

POE-5/POP-12 tallow amine

POE-5/POP-12 tallow amine was tested in rats in a 28-day oral repeated dose toxicity study.[10] This substance is not identified as a cosmetic ingredient in the INCI Dictionary. However, POE-5/POP-12 tallow amine is a likely analog for PEGs cocamine and related ingredients in a read-across assessment. Groups of 5 male and 5 female CD rats received 0, 15, 75, or 200 mg/kg/day POE-5/POP-12 tallow amine by gavage for 28 days. There were no unscheduled deaths in this study. Increased salivation among the rats in the 75 mg/kg/day and 200 mg/kg/day groups was attributed to the taste of the test material. Noisy respiration in some of the females receiving 200 mg/kg/day was not associated with effects observed at necropsy and, therefore, was not considered to be toxicologically significant. Likewise, occasional brown staining around the muzzle at 75 mg/kg/day and 200 mg/kg/day was not considered toxicologically significant. At 200 mg/kg/day, mean body weight, body weight gain, and food consumption were reduced in both males and females, compared with controls. Reduced body weight gain was also observed in males at 75 mg/kg/day. No treatment-related or toxicologically significant changes in hematological or clinical chemistry parameters were found in this study. Increases in absolute and relative adrenal weights in both males and females at 200 mg/kg/day were not accompanied by microscopic findings and were, therefore, not considered to be toxicologically significant. The NOAELs reported for this study were 75 mg/kg/day (males) and 200 mg/kg/day (females), and the LOAEL was 200 mg/kg/day (males) based on reduced body weight, body weight gain and food conversion efficiency.

Dermal

PEG-2 tallow amine

Two groups of 5 young adult New Zealand White rabbits of each sex were exposed dermally to 0.1% or 0.5% PEG-2 tallow amine dispersed in water.[4,5,9,12,29] The test material was applied to the shaved dorso-lumbar region of each animal, 2.0 ml/day, 5 days/week for 28 days (2 or 10 mg/kg/day). Distilled water (2 ml/kg) was applied dermally to a third group of 5 rabbits of each sex to serve as a control. Each application was left in place for 7 hours before washing. Individual body weights were measured at the beginning of the study and weekly thereafter. All animals were examined for overt toxicity at least once every day, and scored for skin irritation every day in accordance with the Draize procedure. Weights of the adrenal glands, kidneys, lungs, testes, heart, liver and ovaries were measured at necropsy. Histopathological examinations were conducted for all animals in the control and high dose groups, and included examination of the reproductive organs. Three animals of each sex died or were euthanized because of illness before the end of the study; none of these deaths were considered to be attributable to the treatment. No treatment-related effects were found on body weights, organ weights or hematological measurements, and no evidence of systemic toxicity from the clinical and pathology examinations.

PEG-20 tallow amine

In a 28-day study, a group of 10 New Zealand Albino (Dutchland) rabbits (5 of each sex) were treated with an aqueous suspension of PEG-20 tallow amine 5 days/week.[5,9] Initially, the rabbits were treated twice with the 10% solution of the test compound applied to abraded skin. This caused severe erythema, edema, and atonia, and mild-to-severe desquamation of the exposed skin. Thus, the concentration was reduced to 2% w/v, and abrasion was discontinued for the remaining 18 treatments. The skin conditions of these animals improved by day 13, and remained relatively constant throughout the remainder of the study. Distilled water was applied to the abraded skin of 10 control rabbits (5 of each sex) for all 20 treatments. Body weights were measured weekly, and hematological analyses and complete necropsies were performed at the end of the study. Liver and kidney weights were measured, and histopathology examinations were performed for several organs, including the treated skin. No treatment-related effects were observed in the skin of the control animals. Body weight losses were reported for 6 of the 10

PEG-20 tallow amine treated rabbits by the end of the first week of the study, after which a steady weight gain was observed. One animal remained below its initial weight by the end of the study. A normal weight-gain pattern was observed in the controls. No biologically significant, treatment-related hematological effects were observed in the treated animals. Necropsy confirmed treatment-related adaptive, cutaneous morphological alterations of the exposed skin, and microscopic examination revealed epidermal and keratin layer thickening. Liver, kidney and body weights of the treated animals were comparable to those of the controls. Decreased kidney weight in treated females, compared to control females, was not considered to be biologically significant.

In another 28-day study, a group of 10 New Zealand white rabbits (5 of each sex) were treated with 2 ml/kg of a 2% w/v aqueous suspension of PEG-20 tallow amine 5 days/week.[5,9] Distilled water was applied to the abraded skin of 10 control rabbits (5 of each sex). The back of each animal was clipped and abraded before the first treatment and every 3 to 4 days throughout the study before the application of the test suspension. Skin abrasion was discontinued when dermal fissures appeared. All rabbits were examined daily for gross signs of toxicity and for mortality. Skin irritation was scored daily in accordance with the Draize method. Individual body weights were measured at the beginning of the study and weekly thereafter. Hematological analyses and complete necropsies were performed at the end of the study. Liver and kidney weights were measured, and histopathology examinations were performed for several organs, including the treated skin and the reproductive organs. Signs of irritation appeared in the treated animals by the end of the first week of the study, and became more pronounced in all of the treated animals during the second week. The signs included moderate-to-severe erythema and edema, slight-to-moderate atonia, slight-to-marked desquamation, moderate leather-like appearance, and slight-to-severe fissuring of the exposed skin. Mild-to-moderate hyperplasia of the epidermis and mild inflammatory changes of the outer dermis were observed on microscopic examination. No dermal irritation was observed in the control group. No statistically-significant differences in body weights, organ weights, or hematological measurements were found in the treated rabbits, compared with controls.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, it was considered unlikely that the PEG cocamine compounds would cause reproductive or teratogenic effects based on their structural characteristics. In subchronic and chronic feeding studies, PEG-6-32 and PEG-75 did not induce reproductive effects in rats.[2]

PEG-2 cocamine

In a combined repeated dose toxicity study and developmental and reproductive toxicity (DART) screening test, groups of 24 Crl:CD(SD) rats (12 males and 12 females) were fed diets containing 0, 30, 100, 300, or 2000 ppm PEG-2 cocamine for 14 consecutive days prior to mating (males and females) and throughout gestation and day 4 of lactation (females).[10] The dietary concentrations tested in this study corresponded to dose rates of approximately 0, 2, 8, 23 and 134 mg/kg/day for males and 0, 3, 9, 26, and 148 mg/kg/day for females. Parental rats were sacrificed about 2.5 weeks after lactation day 4, and the offspring were sacrificed on lactation day 4. There were no treatment-related mortalities. Rats of the 2000 ppm group exhibited increased incidences of red material around the nose, reddened nose, and reddened mouth. At 2000 ppm, mean body weight was reduced (during the first week of treatment), food consumption was reduced (throughout the study), and males exhibited reduced liver, kidney, thyroid, and heart weights, which were attributed to the reduction in body weight. The females of the 2000 ppm group displayed a reduced number of implantation sites and live litter size. The offspring of this group had lower postnatal survival on post-natal days 0, 1, and 4 (and over the period of birth to post-natal day 4) compared to the controls. No treatment-related effects were observed at any of the concentrations tested in male and female mating and fertility, male copulation and female conception indices, gestation length, functional observation test battery, locomotor activity, hematology, or serum chemistry. No treatment-related effects were found in the parental animals or their offspring at 30, 100, or 300 ppm. The NOAEL was 300 ppm (23 to 16 mg/kg/day) for parental and developmental effects and 2000 ppm for reproductive effects in this study. The LOAEL was 2000 ppm for parental and developmental effects.

PEG-15 tallow amine

In a developmental toxicity study, groups of 25 female Charles River Crl:CDBr rats received 0 (corn oil only), 15, 100 or 300 mg/kg/day PEG-15 tallow amine by gavage from day 6 through 15 of gestation.[10] Developmental parameters measured included numbers of viable fetuses, early and late resorptions, total implantations, total *corpora lutea*, as well as the sex and weight of the fetuses. The fetuses were examined for external, visceral and skeletal anomalies and abnormalities. Six of the females of the 300 mg/kg/day group died during gestation. Clinical signs found in the 300 mg/kg/day group included rales, labored respiration, yellow urogenital or anogenital matting and mucoid feces. None of the control animals exhibited these effects, and the animals of the 15 mg/kg/day and 100 mg/kg/day groups exhibited few or no clinical signs. Body weight, body weight gain, and food consumption were reduced in the 300 mg/kg/day group, but not in the 15 mg/kg/day and 100 mg/kg/day groups (except for a transient statistically-significant reduction in food consumption in the 100 mg/kg/day group). Gravid uterine weight was not affected by treatment, and no treatment-related effects were found on liver weight or gross pathology of the dams at any of the dose rates tested. The mean number of malformations in the fetuses of the 300 mg/kg/day group appeared to be high, but most of the malformations were found in a single fetus. Among the fetuses of the 300 mg/kg/day group, one was missing a urinary bladder, one exhibited stenosis of the right carotid artery, two had *situs inversus*, and one had vertebral anomalies. These effects were not considered to be treatment related because *situs inversus* was seen also in one of the control fetuses, and the incidences of all of the other effects were within the ranges of historical controls. No malformations were observed in the 15 mg/kg/day and 100 mg/kg/day groups. Several skeletal variations of the sternebrae and ribs were observed in the fetuses of these groups, as well as in the control group, and were not considered to be treatment related. The maternal NOAEL was 100 mg/kg/day and the developmental NOAEL and maternal LOAEL was 300 mg/kg/day in this study.

In a 2-generation DART screening study, groups of 40 CD (Sprague-Dawley) rats (20 males and 20 females per group) were fed a diet containing 100, 300 or 1000 ppm PEG-15 tallow amine, and a similar group of control rats received the basal diet only.[10] The parental animals of the first generation (F_0) were exposed to the test substance for at least 70 days before mating, and exposure continued until these animals were sacrificed; female F_0 rats were sacrificed on postnatal day (PND) 21 of the F_1 generation. Weanling F_1 animals were fed test diets yielding dose rates of approximately 0, 6, 18, or 61 mg/kg/day (males) or 0, 7, 22, or 74 mg/kg/day (females) PEG-15 tallow amine until PND 70. The F_1 animals selected for breeding from the high-dose group were fed 1000 ppm PEG-15 tallow amine in the diet for at least 80 days before they were mated. All parental/adult animals were examined for mortality, clinical signs, reproductive function, fertility, mating performance, macroscopic abnormalities, and histopathological findings, and body weights, body weight gains, food consumption, and absolute and relative organ weights were measured. Blood samples were collected from one F_1 male and one F_1 female per litter at necropsy to measure testosterone and/or thyroid hormone concentrations. Sperm from all F_1 males were evaluated for motility and morphology at termination. Factors evaluated in the F_1 and F_2 generations included litter size, viability, clinical signs, body weights, body weight gains, developmental (sexual and physical) parameters, and macroscopic abnormalities at necropsy. Potential treatment-related effects were observed in the F_0 females and F_1 litters, including litter loss, increased mean number of unaccounted-for implantation sites, decreased mean number of pups born, live litter size, and postnatal survival. These effects were observed only in a small number of litters, were not always statistically significant, and were not observed in the F_2 litters. However, the statistically significant increase in the mean number of unaccounted-for implantation sites exceeded the maximum mean of laboratory historical control data. The NOAEL for systemic effects and the LOAEL for developmental and reproductive effects was 1000 ppm (65 to 66 mg/kg/day), and the NOAEL for developmental and reproductive effects was 300 ppm (15 to 17 mg/kg/day) in this study.

GENOTOXICITY

PEG- 15 Cocamine was tested for mutagenicity using the paper-disk method. Nutrient agar was seeded with streptomycin dependent Sd-4-73 Escherichia coli and filter-paper disks containing PEG-15 Cocamine were placed on the surface of the cultures. The frequency of reversion from streptomycin dependence to independence was used as the measure of mutagenicity. PEG- 15 Cocamine was negative in this test.[2]

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.[2]

Table 11 summarizes 10 genotoxicity studies of several PEGs cocamine ingredients and one ingredient analog (ie, PEG-8 stearamine), including 7 *in vitro* tests (PEG-2 tallow amine, PEG-8 stearamine, PEG-15 tallow amine, and PEG-20 tallow amine) and 3 *in vivo* tests (PEG-2 tallow amine, PEG-15 tallow amine and PEG-20 tallow amine). The results were generally negative, except that one of the 4 *in vitro* tests of PEG-20 tallow amine

produced a concentration-dependent (0.05 to 0.3 µl/ml) increase in the numbers of chromosome aberrations in Chinese hamster ovary cells with metabolic activation.[9]

In addition, an acute dosage of PEG-2 tallow amine (10,860 mg/kg by gavage) in a mouse micronucleus (MN) test yielded a statistically-significant increase in the number of micronucleated polychromatic erythrocytes 24 hours (but not 48 or 72 hours) after exposure, as well as overt signs of toxicity.[9] The increase in micronucleated cells at 24 hours was not considered to be treatment related because the increase was well within the range of historical controls. However, the ratio of polychromatic to normochromatic erythrocytes was statistically-significantly reduced 24, 48 and 72 hours after exposure to the test substance, suggesting treatment-related toxicity to bone marrow cells at the dose tested.

CARCINOGENICITY

PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously. All of the carcinogenicity data available on the PEGS were 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 ([0.3 ml/week], *30 weeks of dosing), intraperitoneally to rats (*[0.25 ml/week], *6 months of dosing), subcutaneously (*[0.25 ml/week]; *20 weeks of dosing to rats;* [0.2 ml/week], *1 year of dosing to mice), or when injected* [0.05 ml] *into the gastric antrum of guinea pigs over a period of 6 months.*[2]

IRRITATION AND SENSITIZATION

PEG-2 cocamine was classified as a moderate cutaneous irritant, and PEG-15 cocamine was considered a mild irritant. PEGs were nonirritating to the skin of rabbits and guinea pigs, and PEG-75 was not a sensitizer, PEG-2 cocamine was considered an ocular irritant, and PEG-15 cocamine caused corneal irritation. 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. Bar soaps containing 13% coconut oil, when tested using Draize procedures, produced minimal skin reactions.[2]

Non-Human

PEG-2 oleamine

Groups of 10 Hartley guinea pigs of each sex were used to test the dermal sensitization potential of PEG-2 oleamine in accordance with the Magnusson and Kligman maximization method.[30] Groups of 5 guinea pigs of each sex served as negative controls. On day 1 of the study, each treated animal received 2 intradermal injections of 0.1% PEG-2 oleamine in corn oil, 2 injections of 0.1% PEG-2 oleamine in Freund's Complete Adjuvant (FCA; 50% in 0.9% NaCl), and 2 injections of FCA (50% in 0.9% NaCl) into the clipped, intercapsular area of the skin (3 cm x 2 cm). Each control animal received 2 injections of corn oil and 4 injections of FCA (50% in 0.9% NaCl). On day 8, filter paper (8 cm^2) saturated with 10% PEG-2 oleamine in ethanol/water (80/20) was applied to the intercapsular area of each treated animal, and left in place for 48 hours under an occlusive dressing. Control animals were similarly exposed to ethanol/water (80/20) during this part of the induction phase. On day 22, all animals (treated and controls) were challenged with the filter paper of Finn chambers saturated with 1% PEG-2 oleamine in acetone applied to the shaved skin of the left and right posterior flanks. The chambers were removed 24 hours after application, and the animals were evaluated 24 and 48 hours later. Marked local reactions at the intradermal injection sites were noted in a few of the treated animals between days 21 and 25 of the study. Discrete erythema (grade 1) was observed in 2 of the 10 animals 48 hours after removing the Finn chambers during the challenge phase. However, there was no evidence of sensitization in any of the treated animals. In a separate group of 15 guinea pigs (10 treated and 5 controls), a positive control substance (1% mercaptobenzothiazole) yielded the results expected. The authors concluded that PEG-2 oleamine does not induce delayed contact hypersensitivity in guinea pigs.

PEG-2 tallow amine (

Five young adult New Zealand White rabbits of each sex were treated with 0.1% or 0.5% PEG-2 tallow amine dispersed in water.[4,5,9,12] The test substance was applied to the shaved dorso-lumbar region of each animal, 2.0 ml/day, 5 days/week for 28 days. Each application was left in place for 7 hours before washing. All animals were examined and scored for skin irritation every day in accordance with the Draize procedure. Skin irritation

appeared in all animals of the 0.5% group within 24 hours after the first exposure, and persisted thereafter throughout the study. Slight erythema and edema after the first treatment was followed by moderate erythema after the second treatment in most of the rabbits of this group. The rabbits in the 0.5% group exhibited slight-to-moderate fissuring, atonia, and wrinkling of the skin and slight desquamation during the first half of the study, except that a thick layer of skin in one of the animals in this group prevented the development of edema and atonia. One rabbit in the 0.5% group developed an acute inflammatory reaction at the exposure site and died during the study. Five of the 10 rabbits in the 0.1% group exhibited slight edema two days after the initiation of treatment, and 2 of these 5 animals developed moderate erythema within 5 days of treatment. Slight edema, desquamation and wrinkled skin were observed in most animals of the 0.1% group. A few rabbits in the control group exhibited minor histological anomalies in the skin at the application site.

PEG-2 tallow amine did not induce sensitization in guinea pigs in a test for delayed contact hypersensitivity.[31] In this test, 20 guinea pigs were topically exposed to 2.6% PEG-2 tallow amine in ethanol during the induction phase, and to 0.6% PEG-2 tallow amine in acetone during the challenge phase. There were 10 control guinea pigs. No other details about the test protocol were provided. The 2.6% solution was irritating to some of the animals during the induction phase (ie, irritation scores ranged from 0 to 2), but 0.6% in acetone was not irritating at challenge (ie, irritation scores of 0). There was no evidence of sensitization during the challenge phase.

In contrast, PEG-2 tallow amine appeared to be sensitizing to mice in a local lymph node assay (LLNA).[31] In this test, 0.1%, 0.3%, or 1.0% PEG-2 tallow amine, or 0.25% dinitrochlorobenzene (DNCB), 50% (v/v) hexyl cinnamal (HCA), or 25% sodium lauryl sulfate (SLS) was applied topically once daily to the dorsum of the ear for three consecutive days (w/v, except where indicated; solvent not specified). PEG-2 tallow amine exposure was associated with a substantial increase in ear thickness and a dose-dependent increase in lymph-node cell proliferation (maximum stimulation index [SI] = 125.9; EC3 < 0.1%). In comparison, the known sensitizers DNCB and HCA yielded SIs of 104.6 and 30.1, respectively. Treatment with the higher doses of PEG-2 tallow amine (ie, 0.3% and 1.0%) or either of the positive control substances was associated with substantially increased B cell to T cell (B:T) ratios and percentages of Ia+/CD69+ cells. Treatment with SLS produced substantial ear swelling and an SI of 3.2, but no increase in cellular markers. The summary states that, although PEG-2 tallow amine was very irritating, the magnitude of the cellular responses indicate that dermal application of this substance may be sensitizing.

Human

PEG-15 cocamine

Two human repeat insult patch tests (HRIPTs) were submitted for PEG-15 cocamine.[4,32,33] In one of these tests, an adult sunscreen formulation containing 2.9% PEG-15 cocamine was not sensitizing in 201 subjects (no details were provided).[33]

In the other test, a leave-on hair styling formulation containing 1.0% PEG-15 cocamine was not sensitizing in 212 subjects.[32] During the induction phase of the study, the formulation was applied neat to the skin of normal subjects, and the application site was covered with a semi-occlusive patch for 24 hours. This was repeated every 48 hours for a total of 9 applications. The ninth application was followed by a 10- to 15-day rest period, and then a challenge phase initiated during the sixth week of the study. The patch was removed 24-hours after the application of the test material, and the sites were graded 48 and 72 hours after application. There were no adverse events reported, and no evidence of sensitization in this study.

PEG-5 soyamine

A hair dye formulation containing 3.4% PEG-5 soyamine caused transient mild-to-moderate signs of irritation in an open application patch test.[34,35] A single 0.5 ml of the undiluted formulation was applied to the inner forearm of each of 12 healthy subjects (10 women and 2 men), followed by rinsing the application site with running tap water for 30 seconds. Irritation, which was attributable to the peroxide/persulphate content of the formulation, was observed 30 minutes and 1 hour after the exposure period, and resolved completely within 24 hours.

Phototoxicity/Photosensitization

Summary data from a photoallergy study (116 subjects) and a phototoxicity study (22 subjects) were submitted to CIR in 2011.[4,37,38] In these studies, no photoallergic or other phototoxic effects were found in the skin

after exposure to an adult sunscreen formulation containing 2.9% PEG-15 cocamine (no details of these studies were provided).

APPLICATION OF THE FRAMEWORK TO EVALUATE PEGS COCAMINE INGREDIENTS

The framework for identifying and evaluating analogs applied in this safety assessment is described and explained in several publications,[3,7,36,37] including one paper that illustrates the application of the framework for assessing the safety of the PEGs cocamine ingredients that are specifically derivatives of coconut oil.[7] The read-across analysis evaluated by the Panel covers the entire group of PEGs cocamine and related ingredients, including the derivatives of soy and rapeseed oil and tallow and the other fatty acids from which the ingredients of this group are manufactured.

Analog Selection

There are substantial differences in physicochemical properties, potential reactivity, and possibly metabolism across the PEGs cocamine and related ingredients. Thus, the group was divided into discrete subgroups, each with its own spectrum of analogs, for the initial assessment.

In accordance with guidance from a medicinal chemist, the initial subgrouping was based primarily on the ethylene glycol chains, rather than the fatty-amine chains, because of the potential impact of the ethoxy chains on physicochemical properties, reactivity, and metabolism. The potential impact of the amine-chain lengths was not ignored, but was considered secondarily.

Another important criterion during this early stage of analog selection was based on evidence in the literature on ethylene glycol indicating that PEG chains >8 ethoxy (EO) units are not metabolized. Thus, it was important to separate the shorter PEGs cocamine ingredients from longer PEGs cocamine ingredients at the EO = 8 break point, at least initially.

Four PEGs cocamine were selected as the structures of interest (SOIs) to cover the range of PEG side-chain lengths for identifying analogs. The alkyl-amine chain length and degree of unsaturation were considered when evaluating the suitability of the analogs identified for each of these four PEGs cocamine. The four PEGs cocamine selected as SOIs are:

- PEG-2 cocamine (Analog Group 1)
- PEG-4 cocamine (Analog Group 2)
- PEG-10 cocamine (Analog Group 3)
- PEG-15 cocamine (Analog Group 4)

Figures 4 through 11 present representative structures for each SOI and the corresponding analogs identified for each group. The structures of ingredients that are listed in the *International Cosmetic Ingredient Dictionary and Handbook* are red in these figures, to distinguish them from the structures of analogs that are not ingredients. Some of the analogs lack toxicological data for read across, including PEG-4 cocamine and PEG-10 cocamine.

Many of the analogs are the larger tallow derivatives, rather than the smaller cocamine derivatives, which generally have greater degrees of unsaturation, as well as longer alkyl chain lengths, than the cocamine derivatives. Hydrogenated tallow is saturated, but PEGs hydrogenated tallow amines still have larger alkyl groups than the corresponding PEGs cocamine.

PEG-2 cocamine (Analog Group 1)

The structure of one major component of PEG-2 cocamine is presented in Figure 4:

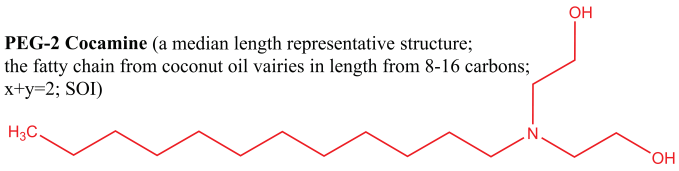


Figure 4. PEG-2 Cocamine (C12)

The structures of the three analogs identified initially for PEG-2 cocamine are illustrated in Figure 5.

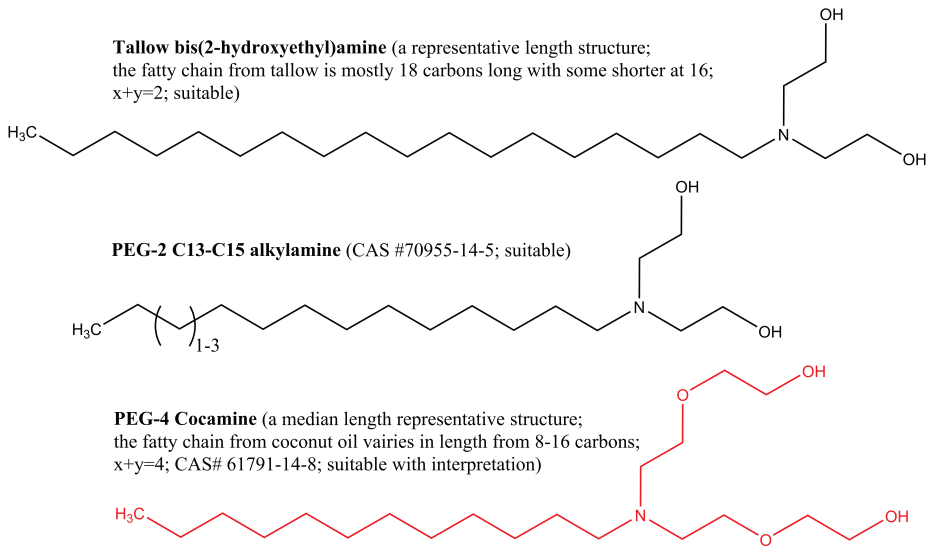


Figure 5. Analogs identified for PEG-2 cocamine

Tallow bis(2-hydroxyethyl)amine (PEG-2 tallow amine) is a "suitable" analog for PEG-2 cocamine because:

- Like PEG-2 cocamine, this analog is not ethoxylated.
- The alkyl chain-length distributions of the analog and PEG-2 cocamine overlap, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.
- The tallow moieties of the analog have greater degrees of unsaturation, and consequently greater susceptibility to epoxidation and hydroperoxidation than the coconut oil moieties of PEG-2 cocamine. Thus, this analog is conservative for PEG-2 cocamine.

PEG-2 C13-C15 alkyl amine is a "suitable" analog for PEG-2 cocamine because:

- Like PEG-2 cocamine, this analog is not ethoxylated.
- The fatty-chain length distribution of the analog is similar to that of PEG-2 cocamine. Differences in the distributions are not expected to cause significant differences in the toxicity profiles of these substances.

PEG-4 cocamine is "suitable with interpretation" for PEG-2 cocamine because:

- The presence of mostly diethoxylate groups in PEG-4 cocamine, rather than the *N*-hydroxyethyl groups of PEG-2 cocamine, may yield divergent metabolic fate and toxicity pathways for these substances.

- The alkyl chain-length distributions of PEG-4 cocamine and PEG-2 cocamine are comparable, and any difference in the distributions would not cause significant differences in the toxicity profiles of these substances.

- The degree of saturation of the alkyl chains of PEG-4 cocamine and PEG-2 cocamine are expected to be comparable.

PEG-4 cocamine (Analog Group 2)

The structure of one major component of PEG-4 cocamine is presented in Figure 6.

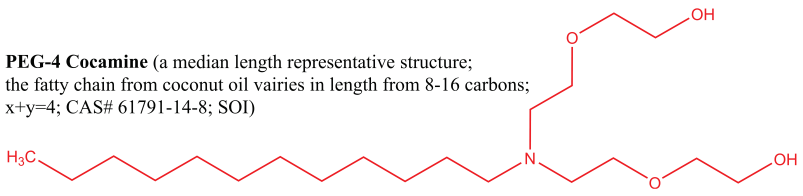


Figure 6. PEG-4 Cocamine (C12)

The structures of the four analogs identified initially for PEG-4 cocamine are illustrated in Figure 7.

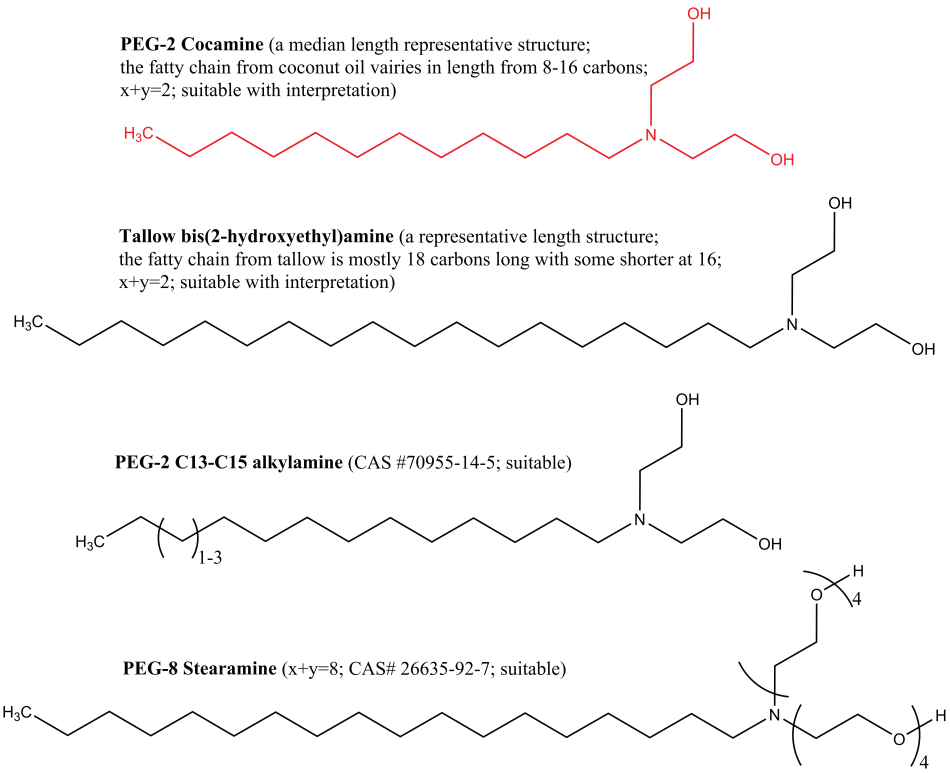


Figure 7. Analogs identified for PEG-4 cocamine

PEG-2 cocamine is "suitable with interpretation" for PEG-4 cocamine because:

- The presence of *N*-hydroxyethyl groups of PEG-2, rather than the diethoxylate groups in PEG-4 cocamine, may yield divergent metabolic fate and toxicity pathways for these substances.
- The alkyl chain-length distributions of the PEG-2 cocamine and PEG-4 cocamine are comparable, and any difference in the distributions would not cause significant differences in the toxicity profiles of these substances.
- The degrees of saturation of the alkyl chains of PEG-2 cocamine and PEG-4 cocamine are expected to be comparable.

Tallow bis(2-hydroxyethyl)amine (PEG-2 tallow amine) is "suitable with interpretation" for PEG-4 cocamine because:

- The presence of *N*-hydroxyethyl groups of the analog, rather than the diethoxylate groups in PEG-4 cocamine, may yield divergent metabolic fate and toxicity pathways for these substances.

- The alkyl chain-length distributions of the analog and PEG-4 cocamine overlap, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.

- The tallow moieties of the analog have greater degrees of unsaturation, and consequently greater susceptibility to epoxidation and hydroperoxidation, than the coconut oil moieties of PEG-4 cocamine. Thus, this analog is conservative for PEG-4 cocamine.

PEG-2 C13-C15 alkyl amine is "suitable with interpretation" for PEG-4 cocamine because:

- The presence of *N*-hydroxyethyl groups of the analog, rather than the diethoxylate groups in PEG-4 cocamine, may yield divergent metabolic fate and toxicity pathways for these substances.

- The alkyl chain-length distributions of the PEG-4 cocamine and PEG-2 cocamine are comparable, and any difference in the distributions would not cause significant differences in the toxicity profiles of these substances.

PEG-8 stearamine is "suitable" for PEG-4 cocamine because:

- Like PEG-4 cocamine, PEG-8 stearamine is ethoxylated, with $x+y \leq 8$

- The alkyl chain-length distributions of PEG-8 stearamine and PEG-4 cocamine are comparable, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.

- The degrees of saturation of the alkyl chains of PEG-8 stearamine and PEG-4 cocamine are expected to be comparable.

PEG-10 cocamine (Analog Group 3)

The structure of one major component of PEG-10 cocamine is presented in Figure 8.

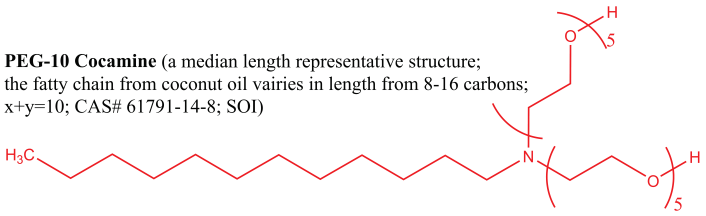


Figure 8. PEG-10 cocamine (C12)

The structures of the four analogs identified initially for PEG-10 cocamine are illustrated in Figure 9.

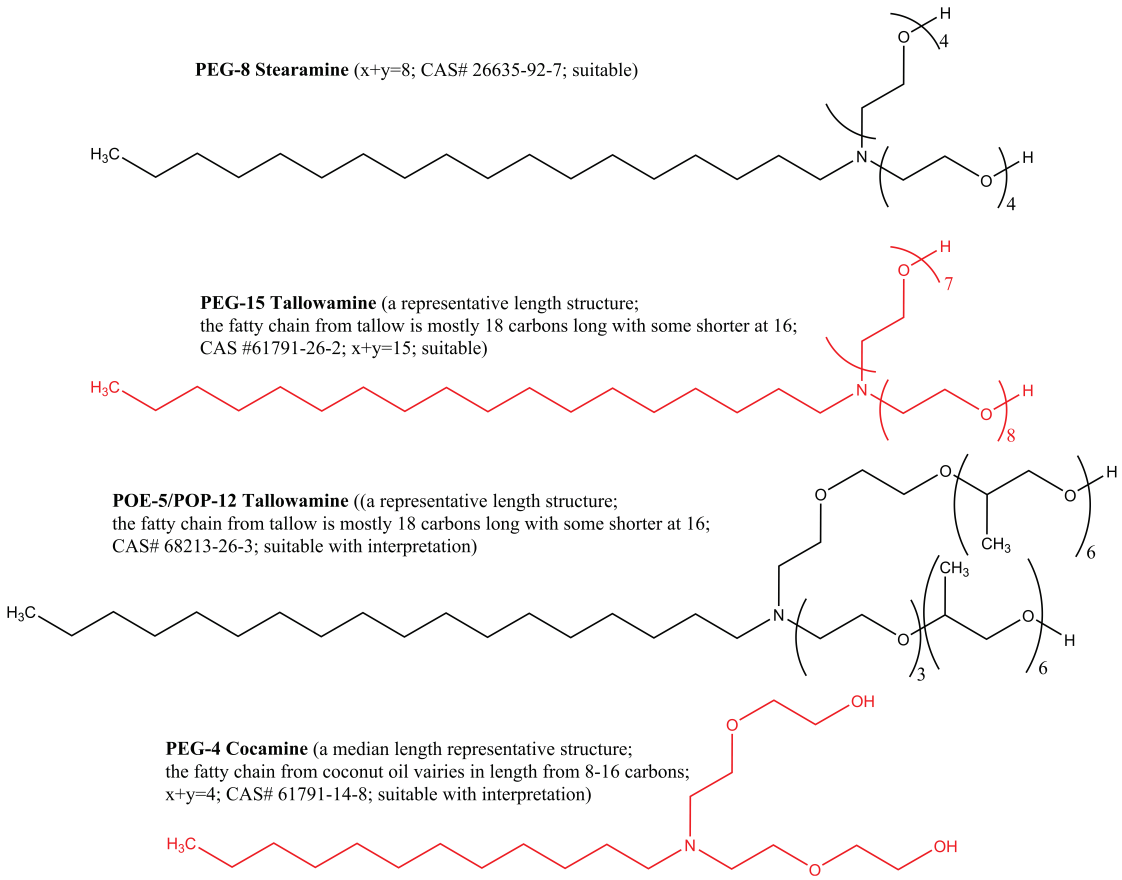


Figure 9. Analogs identified for PEG-10 cocamine

PEG-8 stearamine is a "suitable" analog for PEG-10 because:

- Like PEG-10 cocamine, PEG-8 stearamine is polyethoxylated. Some fraction of PEG-10 cocamine will have $x+y \leq 8$, like the analog.

- The alkyl chain-length distributions of PEG-8 stearamine and PEG-10 cocamine overlap, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.

- The degrees of saturation of the alkyl chains of PEG-8 stearamine and PEG-4 cocamine are expected to be comparable.

PEG-15 tallow amine is a "suitable" analog for PEG-10 cocamine because:

- Like PEG-10 cocamine, PEG-15 tallow amine is polyethoxylated. A larger fraction of PEG-10 cocamine will have $x+y \leq 8$ than the analog. However, this difference is not expected to cause significant differences in the metabolism and toxicity profiles of these substances.

- The alkyl chain-length distributions of PEG-15 tallow amine and PEG-10 cocamine overlap, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.

- The tallow moieties of the analog have greater degrees of unsaturation, and consequently greater susceptibility to epoxidation and hydroperoxidation, than the coconut oil moieties of PEG-10 cocamine. Thus, this analog is conservative for PEG-4 cocamine.

POE-5/POP-12 tallow amine is "suitable with interpretation" for PEG-10 cocamine because:

- The analog has both ethoxyl and propoxyl groups, which will yield substantial differences in physicochemical properties compared with PEG-10 cocamine, but not much impact on reactivity.

- The alkyl chain-length distributions of the analog and PEG-10 cocamine overlap, and differences in the distributions are not expected to cause significant differences in the toxicity profiles of these substances.

- The tallow moieties of the analog have greater degrees of unsaturation, and consequently greater susceptibility to epoxidation and hydroperoxidation, than the coconut oil moieties of PEG-10 cocamine. Thus, this analog is conservative for PEG-4 cocamine.

PEG-4 cocamine is "suitable with interpretation" for PEG-10 cocamine because:

- PEG-4 cocamine has mostly diethoxylate groups, rather than the polyethoxylate groups of PEG-10 cocamine, which may yield divergent metabolic pathways and toxicity profiles.

- The alkyl chain-length distributions of PEG-4 cocamine and PEG-10 cocamine are comparable, and differences in the distributions would not cause significant differences in the toxicity profiles of these substances.

- The degree of saturation of the alkyl chains of PEG-2 cocamine and PEG-4 cocamine are expected to be comparable.

PEG-15 cocamine (Analog Group 4)

The structure of one major component of PEG-15 cocamine is presented in Figure 10.

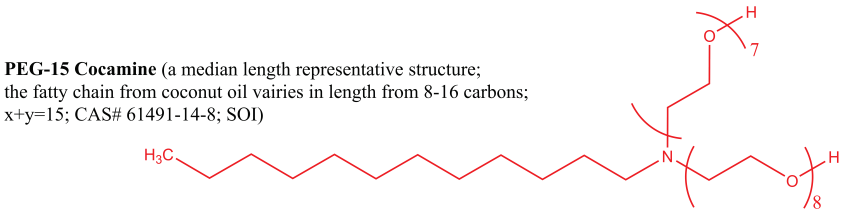


Figure 10. PEG-15 cocamine (C12)

The structures of the five analogs identified initially for PEG-15 cocamine are illustrated in Figure 11.

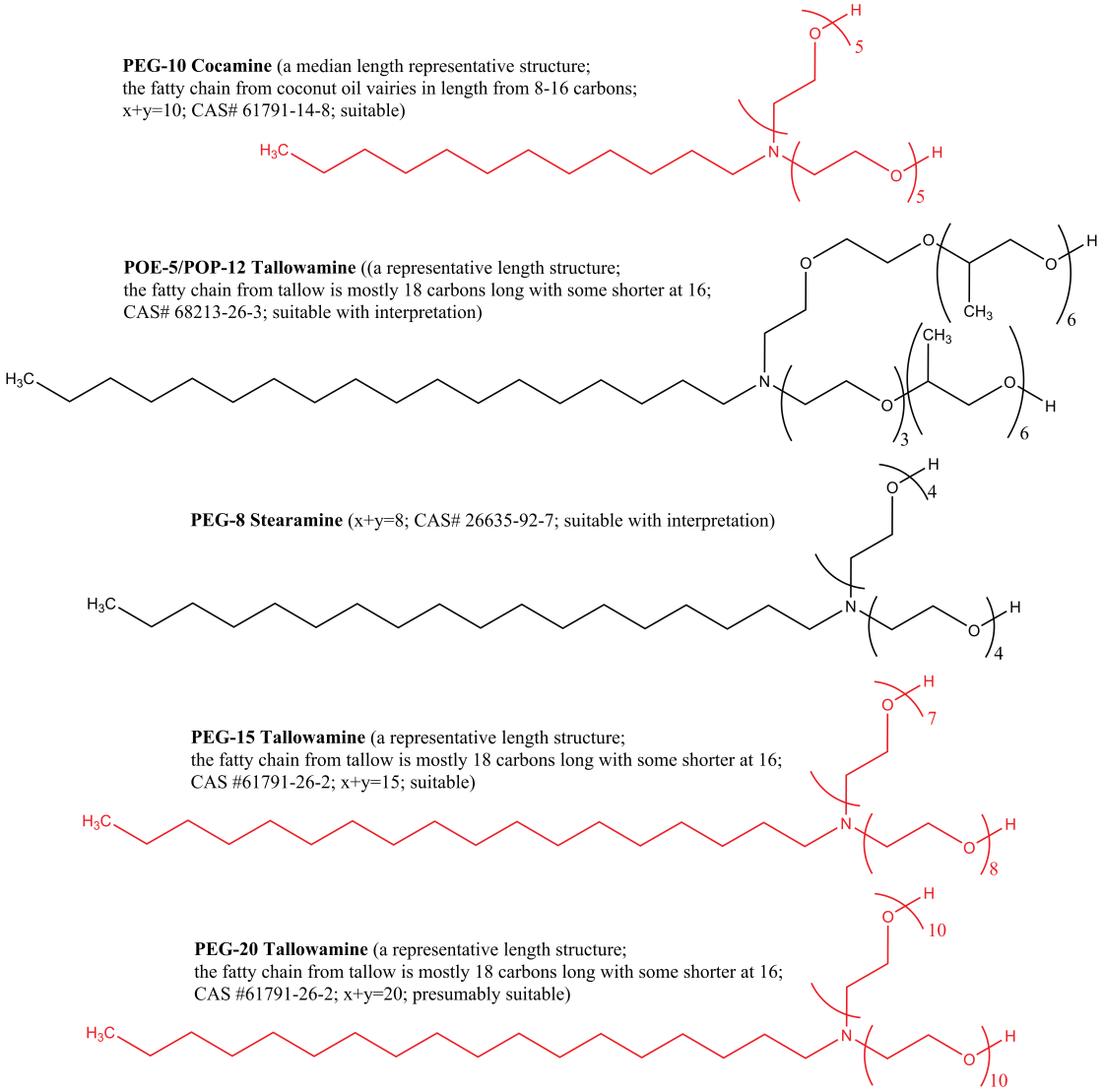


Figure 11. Analogs identified for PEG-15 cocamine

PEG-10 cocamine is a "suitable" analog for PEGs-15 cocamine because:

- Like PEG-15 cocamine, PEG-10 cocamine is polyethoxylated. A larger fraction of PEG-10 cocamine will have $x+y \leq 8$ than PEG-15 cocamine. However, this difference is not expected to cause significant differences in the metabolism and toxicity profiles of these substances.

- The alkyl chain-length distributions of PEG-10 cocamine and PEG-15 cocamine are comparable, and differences in the distributions would not cause significant differences in the toxicity profiles of these substances.

- The degree of saturation of the alkyl chains of PEG-10 cocamine and PEG-15 cocamine are expected to be comparable.

POE-5/POP-12 tallow amine is "suitable with interpretation" for PEG-15 cocamine because:

- The analog has both ethoxyl and propoxyl groups, which will yield substantial differences in physicochemical properties compared with PEG-10 cocamine, but not much impact on reactivity.

- The alkyl chain-length distributions of the analog and PEG-15 cocamine overlap, and differences in the distributions are not expected to cause significant differences in the toxicity profiles of these substances.

- The tallow moieties of the analog have greater degrees of unsaturation, and consequently greater susceptibility to epoxidation and hydroperoxidation, than the coconut oil moieties of PEG-10 cocamine. Thus, this analog is conservative for PEG-4 cocamine.

PEG-8 stearamine is "suitable with interpretation" for PEG-15 cocamine because:

- Like PEG-15 cocamine, PEG-8 stearamine is polyethoxylated. Some fraction of PEG-10 cocamine will have $x+y \leq 8$, like the analog.

- The alkyl chain-length distributions of PEG-8 stearamine and PEG-15 cocamine overlap, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.

- The degrees of saturation of the alkyl chains of PEG-8 stearamine and PEG-15 cocamine are expected to be comparable.

PEG-15 tallow amine is a "suitable" analog for PEG-15 cocamine because:

- Like PEG-15 cocamine, PEG-15 tallow amine is polyethoxylated, with $x+y > 8$.

- The alkyl chain-length distributions of PEG-15 tallow amine and PEG-15 cocamine overlap, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.

- The tallow moieties of PEG-15 tallow amine have greater degrees of unsaturation, and consequently greater susceptibility to epoxidation and hydroperoxidation, than the coconut oil moieties of PEG-15 cocamine. Thus, this analog is conservative for PEG-15 cocamine.

PEG-20 tallow amine was not specified as to a suitability rating, but is most probably a "suitable" analog for PEG-15 cocamine because:

- Like PEG-15 cocamine, PEG-20 tallow amine is polyethoxylated, with x+y > 8.
- The alkyl chain-length distributions PEG-20 tallow amine and PEG-15 cocamine overlap, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.
- The tallow moieties of PEG 20 tallow amine have greater degrees of unsaturation, and consequently greater susceptibility to epoxidation and hydroperoxidation, than the coconut oil moieties of PEG-15 cocamine. Thus, this analog is conservative for PEG-15 cocamine.

Chemical Structure

The SOIs and selected analogs were evaluated for commonality of structural alerts (eg, Ashby alerts for genotoxicity and DEREK for Windows® alerts for several toxicity endpoints), key functional groups and core substructures, as well as for the presence of additional functional groups. This effort showed a satisfactory degree of commonality in structural features and alerts across the SOIs and analogs.

No structural alerts were found for genotoxicity when the SOIs and analogs were evaluated using the DEREK for Windows® and TIMES® prediction models.

The SOIs and analogs with ethoxylated chains consistently yielded a "rapid prototype" DEREK for Windows® alert for nephrotoxicity, which is associated in the software with the structural description of "1,2-ethyleneglycol or derivative." However, as the CIR SSC noted, the specificity of a "rapid prototype alert" is likely to be low. DEREK for Windows® does not reveal the structures of the proprietary ethylene glycol derivatives that led to the development of this rapid prototype alert.

DEREK for Windows® Rapid Prototype Alert Notation

"This alert describes the nephrotoxicity of 1,2-ethyleneglycol and its derivatives. This is a rapid prototype alert derived using a proprietary data set of 731 chemicals, classified on the basis of the presence or absence of histopathologic lesions in the kidney in oral rat repeated-dose studies mostly of 28-days duration. Eleven chemicals in this data set activated this rapid prototype alert and five of these were nephrotoxic."

The rapid prototype alerts are based on a single set of data from one source. They are intended to signal a potential toxicophore, but have not been subjected to the same level of review that is usual for the standard alerts in the DEREK for Windows® knowledge base.

The Panel has evaluated the available data on triethylene glycol and other PEGs with average x+y >2, including the reports of renal toxicity when PEGs have been used on severely damaged skin, as in burn patients.[18] The Panel determined that the PEGs are not metabolized to ethylene glycol, at least under normal homeostasis, and oral and dermal toxicity studies of the PEGs yielded no evidence of the type of nephrotoxicity produced by ethylene glycol and diethylene glycol. PEGs-induced nephrotoxicity has been observed only in patients with severe burns over large surface areas of the body. The Panel concluded that there was no reason for concern for PEGs in rinse-off products, and that there is a large margin of safety for leave-on products containing PEGs, after reviewing PEG-4 dermal penetration data for normal skin and skin in which the stratum corneum was removed.

If the ethoxyl chains are metabolized to yield acid metabolites, then it would be reasonable to anticipate that the PEGs cocamine and related ingredients could cause nephrotoxicity at high doses. However, these materials are so irritating in the digestive tract that they cannot be tested at doses sufficiently high to cause nephrotoxicity.

Physicochemical Properties

There are substantial differences in physicochemical properties across the PEGs-cocamine SOIs and their corresponding analogs. These differences would undoubtedly affect bioavailability in a manner dependent on the route of exposure. The longer alkyl chain-lengths derived from the fatty acids of tallow or hydrogenated tallow and

longer polyethoxy chains are generally expected to reduce bioavailability, compared to the shorter alkyl-chain lengths derived from the fatty acids of coconut oil and shorter polyethoxy chains. However, longer polyethoxy chain-lengths will be associated with greater polarity, which may offset the effect of the greater molecular weight of the tallow-derived analogs to some extent.

Chemical Reactivity

As noted above, the mean chain-length for tallow fatty acids is longer than for coconut oil fatty acids. In addition, the degree of unsaturation is greater in tallow than in coconut oil, but hydrogenated tallow has the lowest degree of unsaturation. Unsaturated fatty acids may form hydroperoxides when autoxidized and epoxides when metabolized.

Another noteworthy difference among the SOIs and analogs is that some of them have *N*-hydroxyethyl side chains (eg, the analog PEG-2 tallow amine) and others have polyethoxyl side chains (eg, the SOI PEG-4 cocamine), as shown in Figure 12.

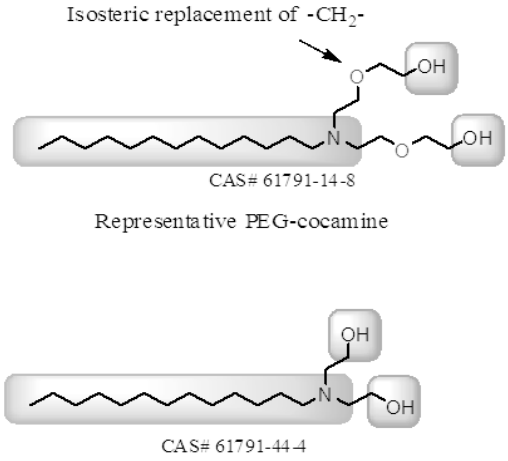


Figure 12. Isostericity of ether and methylene linkages

However, the ether linkage is isosteric with a $-CH_2-$ linkage. Isosteric substituents have similar molecular shapes and volumes, approximately the same distributions of electrons and, thus, would not be expected to be very different in chemical reactivity. Thus, these isosteric groups should have similar toxicology profiles if there is no metabolism (eg, for SOIs and analogs with $x+y > 8$).

Metabolism

There is likely to be some metabolism of the smaller PEGs cocamine and related ingredients (ie, those with $x+y \leq 8$). The CIR SSC and Council member companies evaluated the potential metabolic transformations of the polyethoxyl moieties of the PEGs cocamine based on data for the PEGs from peer-reviewed publications and predictions from the application of computational tools, such as METEOR®. Theoretical metabolic transformations of the PEGs cocamine and related ingredients are illustrated in Figure 13.

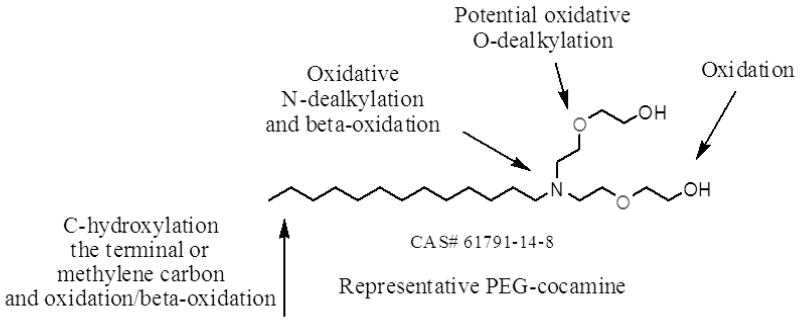


Figure 13. Theoretical metabolic transformations of PEGs cocamine ingredients.

Differences in chemical structure that could affect metabolism across the analogs include the presence of *N*-hydroxyethyl groups in SOIs and analogs for which x+y=2, rather than the *N*-polyethoxyl groups in SOIs and analogs for which x+y≥4. *O*-dealkylation is not possible for PEG-2 cocamine and the analogs lacking *N*-polyethoxyl groups.

The potential for *O*-dealkylation of *N*-polyethoxyl groups of the PEGs cocamine and analogs was addressed through a search of the literature on the metabolism of PEGs.

The metabolism of the polyethoxylate groups in PEGs cocamine is anticipated to be similar to the metabolism of PEGs. PEGs are excreted mainly unchanged in the urine and feces after oral or intravenous exposure.[38,39] The extent of metabolism depends on molecular weight; there is little or no metabolism of PEGs with molecular weights >5000 Da (eg, PEG-100).

The metabolism of PEGs involves oxidation of the terminal alcohol groups to yield carboxylic acids, which is likely mediated by alcohol dehydrogenases or possibly sulfate conjugation of the terminal alcohol groups by sulfotransferases (Figure 14).

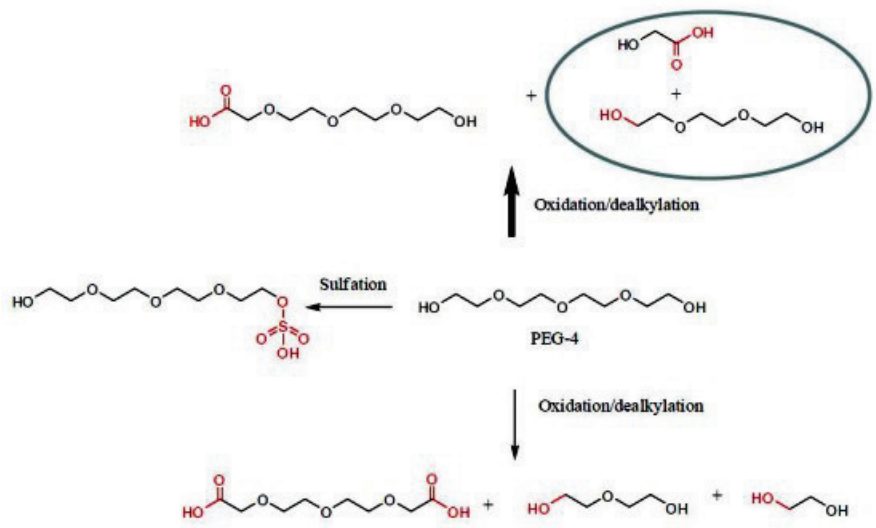


Figure 14. Metabolism of PEGs

However, *O*-dealkylation is not a major route of metabolism. Only very small amounts of oxalic acid are formed from the *O*-dealkylation and alcohol oxidation of PEGs for which x+y=5 to 8 (and no detectable amounts of oxalic acid formed from PEGs for which x+y≥8). Ethylene glycol has not been shown to be formed as a metabolite of the PEGs.

An additional consideration, as noted above, is that the unsaturated fatty acids of tallow (not hydrogenated tallow) in the structure of some of the ingredients and analogs may be metabolized to form epoxide metabolites.

The PEGs-cocamine and related structures that have no unsaturated fatty-acid amine moieties do not have this potential.

None of the final metabolites of PEG-4 cocamine were predicted to be of toxicological concern using computational tools. PEG-4 cocamine was chosen in two studies as a model compound to predict metabolic transformations and toxicity.

In the first of these studies, the structural features of PEG-4 cocamine were examined, and substructure searches and METEOR® were used to predict the metabolic fate of the PEG-4 cocamine having the structure depicted in Figure 15.

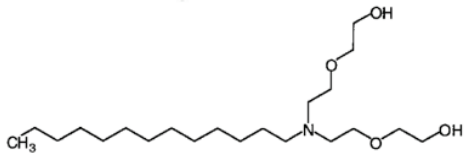


Figure 15. PEG-4 cocamine structure evaluated in the first case study.

PEG-4 cocamine may undergo oxidation, *C*-hydroxylation or *N*-dealkylation to form corresponding metabolites. The possible major metabolic fate of PEG-4 cocamine predicted from this analysis is depicted below, where compound (1) is PEG-4 cocamine.

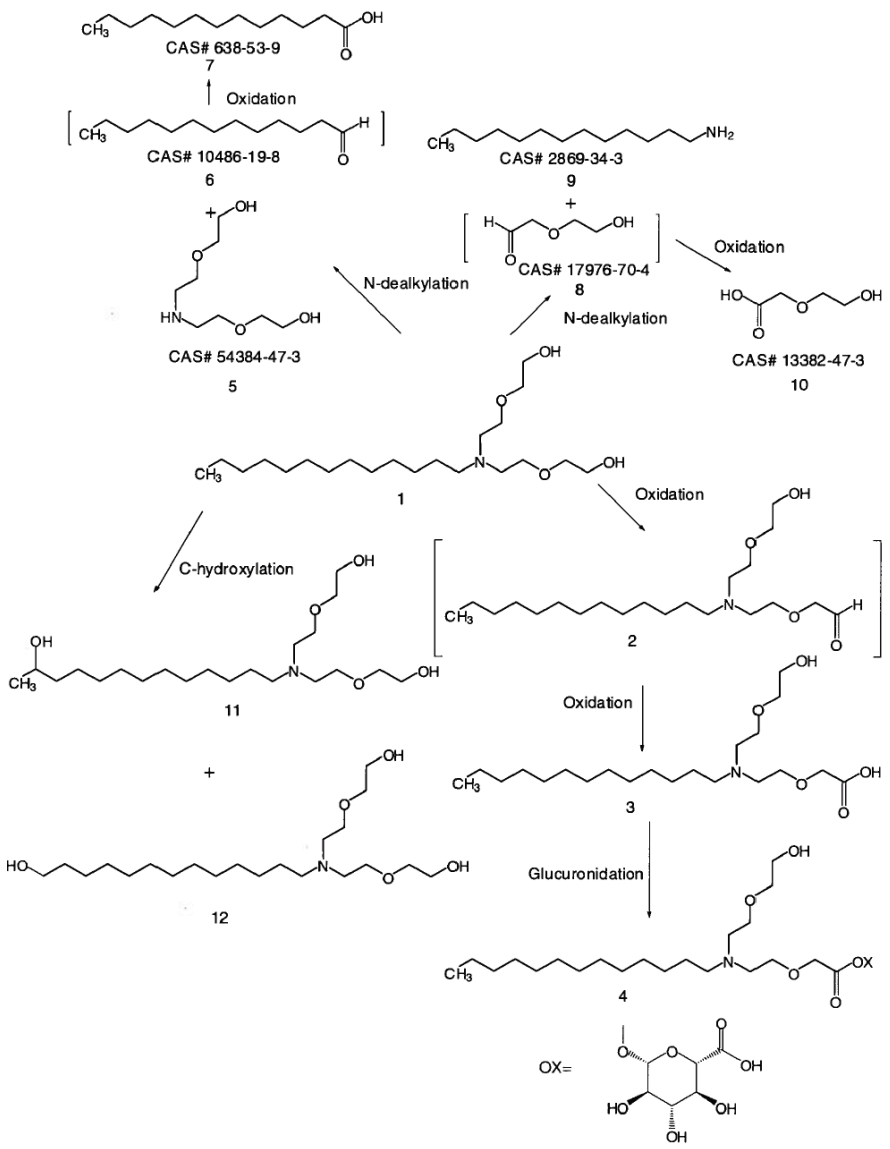


Figure 16. Predicted major metabolites of a PEG-4 cocamine in the first case study.

The oxidation of ethoxyl ethanol may yield the corresponding metabolite (3) through an aldehyde (2) intermediate. The enzymes that catalyze the metabolism of primary alcohols to aldehydes and then to carboxylic acid have broad substrate specificity. Subsequently, the metabolite (3) could be glucuronidated to yield metabolite (4).

The oxidative *N*-dealkylation of (1) may yield metabolites (5), (7) or {9), (10). The formation of metabolites (7) and (10) would proceed through the corresponding intermediate aldehydes (6) and (8). Oxidative *N*-dealkylation (aka deamination) involves hydrogen abstraction and oxygen addition (hydroxylation) at a carbon atom α to the nitrogen atom.

In addition, *C*-hydroxylation reactions of the alkyl chain to yield (11) and (12) are possible. For longer alkyl chains, hydroxylation of a methylene group may occur, as well as hydroxylation at the terminal methyl group.

In the second computational study, the software used included:

- Vitic (http://www.lhasalimited.org/)
- LEADSCOPE (http://www.leadscope.com/)
- OECD Toolbox (http://www.oecd.org)
- METEOR® (http://www.Ihasalimited.org/)
- TIMES® (http://oasis-lmc.org)
- DEREK for Windows® (http://www.lhasalimited.org)
- MC4PC (Multicase) (http://oasis-lmc.org)
- Toxtree (http://ambit.acad.bg)
- VirtualToxLab (http://www.biograf.ch)

The structure of PEG-4 cocamine analyzed in this second study is presented in Figure 17.

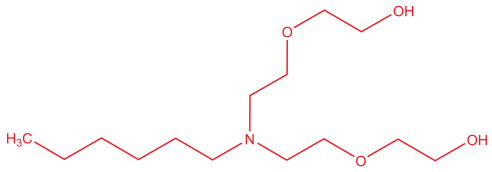


Figure 17. PEG-4 cocamine structure evaluated in the second case study.

The authors noted that PEG-4 cocamine has a MW of 277 and an estimated log P of 1.961, which suggests that its rate of absorption into the skin would be similar to that of ethanolamine.[4] In the skin, PEG-4 cocamine could be metabolized or enter the systemic circulation and the liver unchanged. Plausible metabolic reactions in the skin are depicted below, where:

- UGT = Uridine diphosphate-glucuronyl transferase
- FMOs = Flavin monooxygenases
- ADH = Alcohol dehydrogenases
- ALDH = Aldehyde dehydrogenases

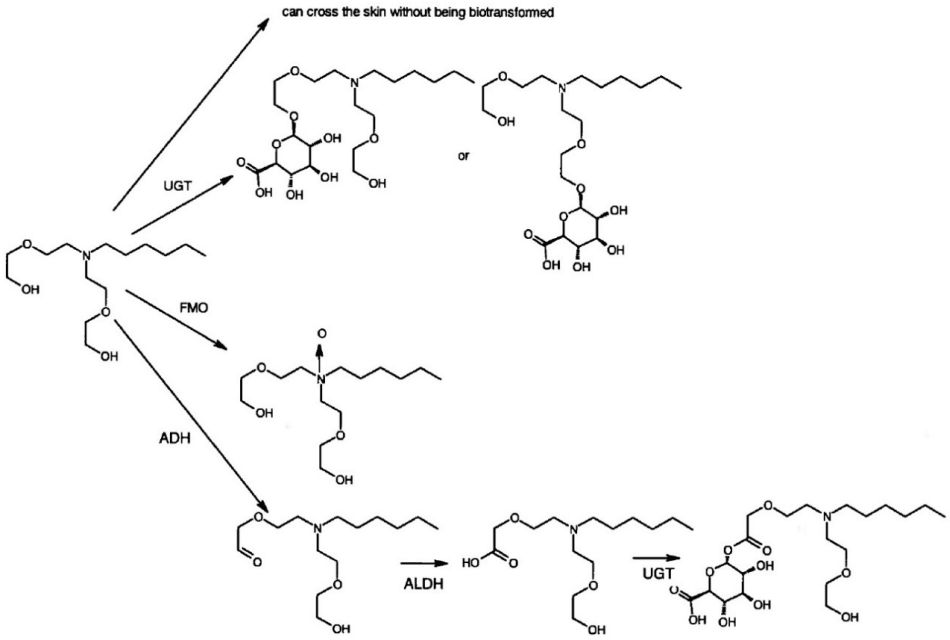


Figure 18. Plausible metabolism of a PEG-4 cocamine in the skin, from the second case study.

N- or *O*-dealkylations are possible, as illustrated below; these are major types of metabolic reactions in the liver, although uncertain in the skin.

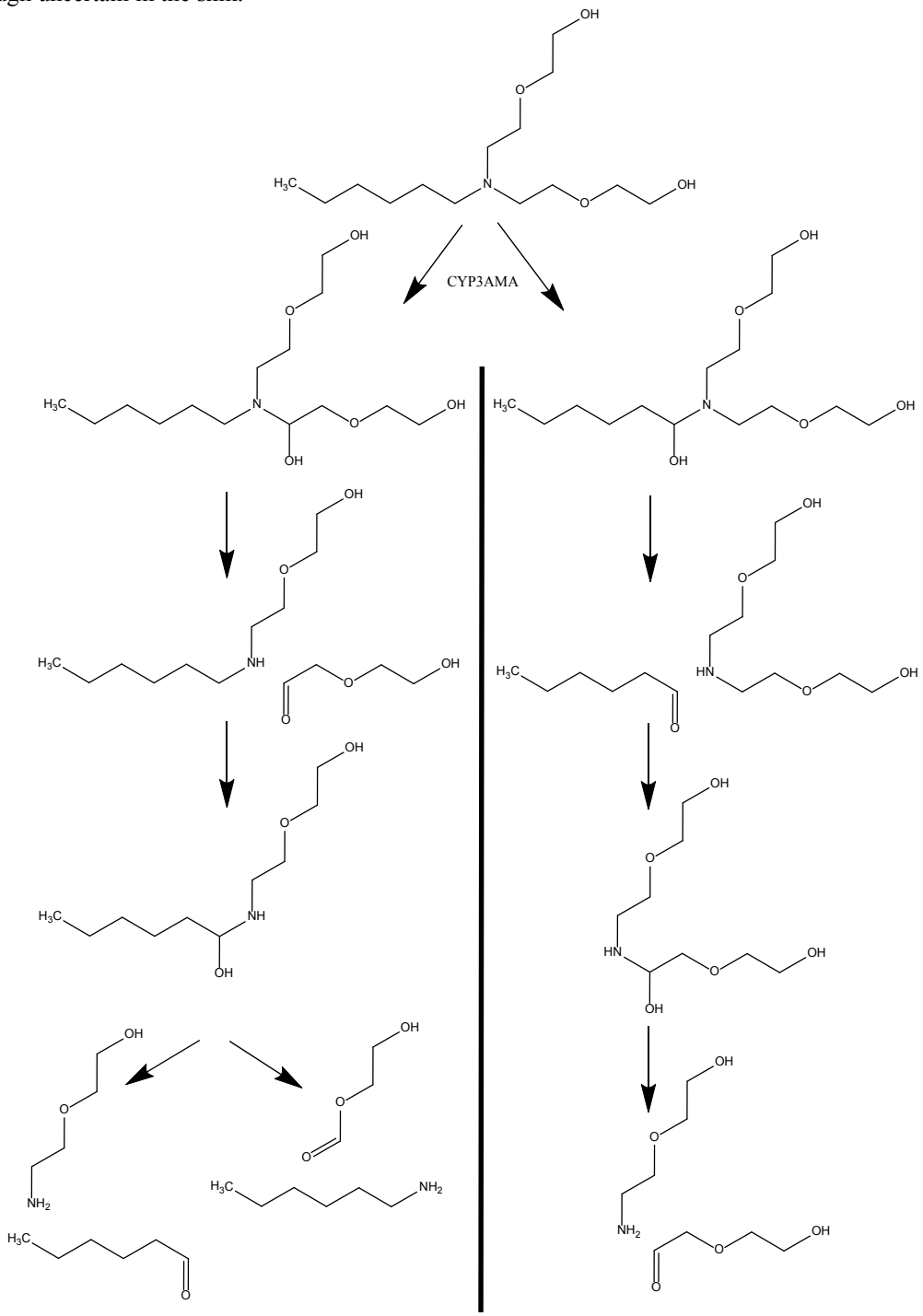


Figure 19. Possible *N*- or *O*-dealkylations in the skin (major in the liver).

Hexanal, if formed via dealkylation (as shown in the figure above) can be metabolized to yield hexanoic acid, which can form a glucuronyl conjugate. Hexamine, if formed, can be oxidized to yield 1,6-hexanediol.

The authors listed the main enzymes expressed in the skin:[4]

- ADH and ALDH are the major mRNA-expressed mRNA Phase-I metabolizing enzymes
- FMO and monamine oxidase A (MAO A) are expressed only at a low level
- Cytochromes P-450 (CYP450s) are expressed at a very low level
- UGTs are Phase-II metabolizing enzymes expressed in the skin, but at a lower levels than glutathione transferases (GSTs), *N*-acetyl transferase (NAT), and catechol-*o*-methyl transferase (COMT)

Other reactions that can occur in the skin and liver include:

- Oxidation of the terminal methyl group of the aliphatic chain
- Oxidative deamination of aliphatic amine

The second study includes a simulation of metabolic transformations in the liver using METEOR® and TIMES®. The primary biotransformations predicted were oxidation and glucuronidation of primary alcohols and dealkylation. TIMES® gives preference to *O*-dealkylation. METEOR® gives preference to *N*-dealkylation (CYP3A3-dependent), which is consistent with the results of *in vitro* and *in vivo* experiments using *N*- or *O*-alkylated compounds.

If an ingredient is available to biotransformation enzymes, an increase in polyethoxy-chain length might increase the potential of the ingredient to interact with enzymes that catalyze *O*-dealkylation. CYPl and 3 families of biotransformation enzymes are expressed at low levels in the skin, but are highly expressed and functional in the liver.

On the other hand, an increase of the fatty-acid chain length would favor β-oxidation, if the compound is available to mitochondrial enzyme systems. The effect of alkyl-chain length on *N*-dealkylation is not known.

The authors noted that metabolism of polymers like the PEGs cocamine and related ingredients could occur at three levels on or in the skin:[4]

- In the skin microflora, if the polymer can penetrate bacteria or fungi and reach oxidative enzymes (there is no information on this topic)
- In the skin, if the molecule can penetrate the skin and contact mitochondrial enzymes (which would enable the oxidation of fatty-acid chains or the *O*-dealkylation of glycol groups)
- In the liver, if the polymer can reach the systemic circulation and the liver

Analog Toxicity Data Review

Tables 12-15 summarize the toxicological data available for the analogs identified for each of the four PEGs cocamine selected as SOIs. The data provided in these tables (and described in greater detail in the appropriate sections of this report) address repeated-dose toxicity, genotoxicity, and DART as toxicological endpoints. Note that a rat DART screening test was identified for PEG-2 cocamine (Tables 12 and 13).

Oral Repeated-Dose Toxicity

Oral repeated-dose toxicity studies, including 28- and 90-day studies, have been conducted in rats and dogs with tallow-derived analogs that cover x+y=2 (ie, three studies for PEG-2 tallow amine) (Tables 12 and 13) and x+y=15 to 17 (ie, two studies, each, for PEG-15 tallow amine and POE-5/POP-12 tallow amine) (Tables 14 and 15). In addition, a 90-day rat study and 90-day dog study of the analog PEG-2 C13-C15 alkyl amine (x+y=2) were performed (Tables 12 and 13). These studies showed local effects on the gastrointestinal tract, but little or no evidence of other treatment-related effects. No evidence of nephrotoxicity was observed in any of these studies. The studies are reasonably consistent in their reported NOAELs or NOELs, given the variety of dose ranges tested in these studies.

The potential differences in chemical reactivity, physicochemical properties, or metabolism of the analogs that were identified during analog evaluation and categorization are not evident in the outcomes of the repeated-dose oral toxicity studies.[5]

Analogs derived from tallow amine comprise the majority of the identified analogs with repeated-dose toxicity data. The greater degree of unsaturation in these analogs, compared with the PEGs cocamine, presents the potential for epoxide formation, suggesting that using these analogs for read-across analysis is a conservative approach to the safety assessment of these ingredients.

In several of the oral studies, histiocytosis (the presence of foamy macrophages) was noted in the small intestines and mesenteric lymph nodes of the test animals. The prevailing scientific opinion is that, without additional evidence of concurrent toxicity, the presence of foamy macrophages in organs such as the intestine should not be considered an adverse effect.[40-43] These lesions are attributable to the clearance of oils with high molecular weight, and are not associated with long-term effects."[41-43] Furthermore, as the authors suggested, histiocytosis in the small intestines and mesenteric lymph nodes observed in a repeated-dose oral toxicity study does not represent well the intended route of human exposure (dermal) for use of the PEGs cocamine ingredients in cosmetic products.[5]

Dermal Repeated-Dose Toxicity

Dermal 28-day repeated-dose toxicity studies have been conducted in rabbits with tallow PEG-2 tallow amine (x+y= 2; one study; Tables 12 and 13) and PEG-20 tallow amine (x+y=20, two studies; Table 15). Local skin irritant effects were noted in these studies, but there was no evidence of systemic toxicity.

Genotoxicity

Both *in vitro* and *in vivo* genotoxicity studies have been conducted with tallow amine analogs (Tables 12-15), including:

- PEG-2 tallow amine (x+y=2); Tables 12 and 13
- PEG-8 stearamine (x+y=8); Tables 13, 14 and 15
- PEG-15 tallow amine (x+y=15); Table 14 and 15
- PEG-20 tallow amine (x+y=20); Table 15

The studies include mammalian and bacterial test systems, and address gene mutation and clastogenicity. The results consistently show an overall lack of evidence of genotoxicity across assays and analogs.

PEG-20 tallow amine was negative in an Ames test, an *in vitro* mouse lymphoma assay, and an *in vitro* unscheduled-DNA synthesis (UDS) assay (Table 15). An *in vitro* chromosome aberration assay for this analog was negative without metabolic activation, but was positive with metabolic activation. However, PEG-20 tallow amine was negative in an *in vivo* chromosome aberration assay in mice (Table 15). The authors also noted that PEG-2 tallow amine (x+y=2) was negative in an *in vivo* mouse micronucleus assay (Tables 12 and 13).[5]

The structure of PEG-4 cocamine shown in Figure 20 was evaluated for potential genotoxicity using the DEREK for Windows® and TIMES® prediction models.

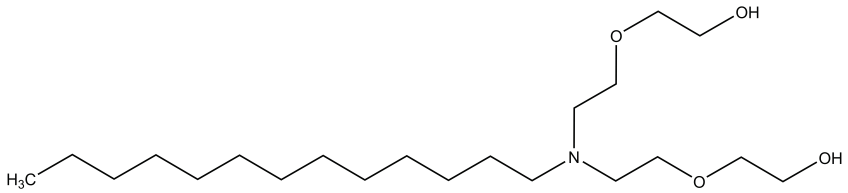


Figure 20. Structure of PEG-4 cocamine evaluated for genotoxicity and sensitization using computational models.

The TIMES® software, in particular, enables the evaluation of liver metabolites likely to be formed from the structure. There were no structural alerts for genotoxicity using the DEREK for Windows® system. In addition, PEG-4 cocamine was predicted to be non-mutagenic and to not be a precursor of chromosomal aberrations using the TIMES® model.

The authors noted that the overall negative results of genotoxicity tests and computational predictions are consistent with the data reported in Appendix A of US EPA Fatty Acid Derived (FND) Amines Category HPV Chemical Challenge.[4,41] The latter presents the results of over 60 genotoxicity tests (including *in vitro*, *in vivo*, bacterial, and mammalian tests) on more than 30 FND amines and FND amides. Only the *in vitro* chromosome aberration assay for PEG-20 tallow amine and one Ames test were positive, among all of these chemicals.

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity data are available for:

- PEG-2 cocamine (x+y=2) Tables 12 and 13
- PEG-15 tallow amine (x+y=15); Tables 14 and 15

No evidence of a teratogenic effect was observed in any of the studies. Reproductive toxicity studies of the analogs showed effects on reproductive performance at doses that were generally comparable to doses causing maternal toxicity. In the reproductive studies, the findings included smaller litter size and reduced body weight. In one of these studies, the effects were associated with frank maternal toxicity.

Dermal Sensitization

An evaluation of the PEG-4 cocamine structure illustrated in Figure 20, using the TIMES®, indicated that this ingredient has the potential to be a weak sensitizer, because of potential formation of hydroperoxides by autoxidation of the ethoxylate chains.

This result is consistent with a report that ethoxylated alcohols were susceptible to autoxidation when exposed to air at ambient temperatures, in daylight, with stirring for 1 hour four times a day for 18 months. [44] Hydroperoxides were the primary oxidation products formed.

The potential for peroxide formation in PEGs has been considered by the Panel, and some literature on the quantitation of peroxides in PEGs of various molecular weights has been cited in CIR safety assessment reports.[16,18] In the Amended Safety Assessment for triethylene glycol and polyethylene glycols, the Panel concluded that the PEGs were not sensitizers in individuals with normal skin, and that sensitization is not a significant concern in individuals with damaged skin.[18]

No other alert for sensitization potential was noted in the PEGs cocamine structure. The PEG-4 cocamine structure mentioned above was also predicted to be non-mutagenic, not a precursor of chromosomal aberrations and not phototoxic, using TIMES®.

SUMMARY

In a report published in 1999, the CIR Expert Panel found that the data were insufficient to support a safety assessment of several PEGs cocamine ingredients. Among the data gaps identified, data specifically on PEG-2 cocamine were needed to demonstrate that relevant exposures to the ingredient with the lowest molecular weight in this group would not be toxic.

In 2011 and 2012, the CIR SSC presented information to the CIR, contending that these data needs can be met through the application of an SAR-based framework for identifying and evaluating structural analogs for read-across assessments. The framework is based on the assessment of SARs, and enables the incorporation of information from the literature and from predictive computational tools on physicochemical properties, chemical reactivity, metabolism and toxicity to identify suitable analogs and develop an overall weight-of-evidence safety assessment.

The PEGs cocamine and related ingredients represent a series of mixtures of mostly tertiary amines that have alkyl groups derived from plant or animal fatty acids and an average number of polyethylene glycol groups equal to the number in the chemical name. The structures of the smallest members of the group (eg, PEG-2 cocamine) may have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, or one hydrogen atom and one *N*-polyethoxyl group. The possibility of similar structural variations is notable for PEG-3, -4, and -5 cocamine and related ingredients. Each PEGs cocamine ingredient is a mixture of compounds with the fatty-acid derived chain lengths ranging from about C6 to C20.

The PEG-n cocamine and related ingredients are manufactured by condensing fatty acid with the ingredient's corresponding number of moles (n) of ethylene. The chain lengths of the PEG groups depend on the duration of the reaction, and these groups may not be symmetrical; typically, this reaction yields a range of PEG chain lengths.

The PEGs cocamine and related ingredients are mixtures of tertiary alkyl amines that may also contain some primary and secondary amines. Thus, nitrosamines can be produced in formulations that contain nitrosating agents. Additionally, the ingredients may contain traces of 1,4-dioxane (which is a by-product of ethoxylation) and ethylene oxide as impurities.

The PEGs cocamine and related ingredients function primarily as surfactants and antistatic agents in cosmetic formulations.

VCRP and industry survey data obtained in 2015 and 2014, respectively, indicate that 10 of the ingredients included in this report are used in cosmetic formulations. PEG-2 rapeseedamine has the most reported uses, with a total of 255 uses in rinse-off hair-coloring preparations. No use concentrations were reported for PEG-2 rapeseedamine. PEG-2 oleamine has the second greatest number of uses, with a total of 254 uses in rinse-off hair-coloring preparations. The highest maximum use concentration for PEG-2 oleamine was 3.5%. Some of the ingredients are reported to be used in body and hand sprays and powder products, and could possibly be inhaled. There were 37 PEGs-cocamine ingredients that do not appear to be in use.

Absorption and metabolism data were not available for the PEGs cocamine ingredients.

The oral LD_{50} of PEG-15 cocamine in rats was 1.2 g/kg, and the LD_{50} of PEG-2 cocamine ranged from 0.75 g/kg to 1.3 g/kg. PEG-2 cocamine was classified as a moderate cutaneous irritant, and PEG-15 cocamine was considered a mild irritant. PEG-2 cocamine was considered an ocular irritant, and PEG-15 cocamine caused corneal irritation.

No dermal sensitization studies were found or submitted for PEG-2 cocamine. In one HRIPT, a hair styling formulation containing 1.0% PEG-15 cocamine was not sensitizing in 212 subjects. In another HRIPT, an adult sunscreen formulation containing 2.9% PEG-15 cocamine was not sensitizing in 201 subjects. Summary data from a photoallergy study (116 subjects) and a phototoxicity study (22 subjects) indicated that there were no photoallergic or other phototoxic effects in the skin after exposure to an adult sunscreen formulation containing 2.9% PEG-15 cocamine (no details of these studies were provided).

PEG-2 oleamine (0.1%) did not induce delayed contact hypersensitivity in a guinea pig maximization test. PEG-2 tallow amine (2.6% ethanol induction phase; 0.6% in acetone challenge) did not induce sensitization in guinea pigs in a test for delayed contact hypersensitivity. In contrast, PEG-2 tallow amine (0.3% or 1%) appeared to be sensitizing, as well as irritating, to mice in a local lymph node assay (LLNA).

PEG-15 cocamine was negative in mutagenicity studies. The CIR safety assessment report published in 1999 indicated that the PEGs cocamine would not be likely to cause reproductive or teratogenic effects, based on their structural characteristics. Accordingly, the parental and developmental NOAELs were 23 mg/kg/day and the reproductive NOAEL was 134 mg/kg/day (highest dose tested) in a DART Screening study using rats in which rats received up 134 mg/kg/day (males) or 148 mg/kg/day (females) in the diet for more than 2 months.

An SAR-based framework for identifying and evaluating structural analogs for read-across assessments was also applied to facilitate the safety assessment of the PEGs cocamine and related ingredients. Four PEGs cocamine were selected as the structures of interest (SOIs) to cover the range of PEG side-chain lengths for identifying analogs, including PEG-2 cocamine, PEG-4 cocamine, PEG-10 cocamine, and PEG-15 cocamine. The analogs identified for these SOIs showed consistent biological responses and yielded comparable NOAELs or NOELs in toxicology studies. In addition, several computational models were used to develop predictions for several major toxicological endpoints, as well as for the potential metabolic fate of the PEGs cocamine, to inform the safety assessment. For example, the PEG-4 cocamine structure was predicted to be a weak sensitizer, using predictive software, because of the potential autoxidation of PEG-4 cocamine to yield sensitizing hydroperoxides.

Many of the analogs identified are the larger tallow derivatives, rather than the smaller cocamine derivatives, which will generally have greater degrees of unsaturation and longer alkyl chain lengths than the cocamine derivatives. The tallow amines are potentially more toxic than the cocamines and the hydrogenated tallow amines because the unsaturated fatty acid moieties are susceptible to epoxidation and hydroperoxidation.

No structural alerts were found for genotoxicity when the SOIs and analogs were evaluated using the DEREK® and TIMES® prediction models.

The SOIs and analogs with ethoxylated chains consistently yielded a "rapid prototype" DEREK® alert for nephrotoxicity, which is associated in the software with the structural description of "1,2-ethyleneglycol or derivative."

If the ethoxyl chains are metabolized to yield acid metabolites, then it would be reasonable to anticipate that the PEGs cocamine and related ingredients could cause nephrotoxicity at high doses. However, these materials are so irritating in the digestive tract that they cannot be tested at doses sufficiently high to cause nephrotoxicity.

There are substantial differences in physicochemical properties across the PEGs-cocamine SOIs and their corresponding analogs. These differences would undoubtedly affect bioavailability in a manner dependent upon the route of exposure. Generally, the longer alkyl chain-lengths derived from the fatty acids of tallow or hydrogenated tallow and longer polyethoxy chains would be expected to reduce bioavailability, compared to the shorter alkyl-chain lengths derived from the fatty acids of coconut oil and shorter polyethoxy chains. However, longer

polyethoxy chain-lengths will be associated with greater polarity, which may offset the effect of the greater molecular weight of the tallow-derived analogs.

Another noteworthy difference among the SOIs and analogs is that some of them have *N*-hydroxyethyl side chains and others have polyethoxyl side chains. However, the ether linkage is isosteric with a -CH2- linkage. Isosteric substituents have similar molecular shapes and volumes, approximately the same distributions of electrons and, thus, would not be expected to be very different in chemical reactivity.

There is likely to be some metabolism of the smaller PEGs cocamine and related ingredients with $x+y \leq 8$. Differences in chemical structure that could affect metabolism across the analogs include the presence of *N*-hydroxyethyl groups in the SOIs and analogs for which $x+y \leq 5$.

The metabolism of the polyethoxylate groups in PEGs cocamine is anticipated to be similar to the metabolism of PEGs. PEGs are excreted mainly unchanged in the urine and feces after oral or intravenous exposure. None of the final metabolites of one PEG-4 cocamine structure were predicted to be of toxicological concern using computational tools.

The toxicological data available for the analogs identified for each of the four PEGs cocamine selected as SOIs can be summarized as follows.

Oral repeated-dose toxicity studies, including 28- and 90-day studies conducted in rats and dogs with tallow-derived analogs or PEG-2 C13-C15 alkyl amine, showed local effects on the gastrointestinal tract, but little or no evidence of nephrotoxicity or other treatment-related effects. In several of the oral studies, histiocytosis was noted in the small intestines and mesenteric lymph nodes. The prevailing scientific opinion is that, without additional evidence of concurrent toxicity, the presence of foamy macrophages in such organs should not be considered an adverse effect. The potential differences in chemical reactivity, physicochemical properties, or metabolism of the analogs, which were identified during analog evaluation and categorization, were not evident in the outcomes of these studies.

Analogs derived from tallow amine comprise the majority of the identified analogs with repeated-dose toxicity data. The greater degree of unsaturation of these analogs, compared with the PEGs cocamine, presents the potential for epoxide formation, suggesting that using these analogs for read-across analysis is a conservative approach to the safety assessment of these ingredients.

Dermal 28-day repeated-dose toxicity studies have been conducted in rabbits with PEG-2 tallow amine and PEG-20 tallow amine. Local skin irritant effects were noted in these studies, but there was no evidence of systemic toxicity.

Both *in vitro* and *in vivo* genotoxicity studies have been conducted with tallow amine analogs. The results consistently showed an overall lack of genotoxicity across assays and analogs. There were no structural alerts for genotoxicity, and PEG-4 cocamine was predicted to be non-mutagenic and to not be a precursor of chromosomal aberrations using computational methods. The overall negative results of genotoxicity tests and computational predictions are consistent with the data reported for more than 60 genotoxicity tests on more than 30 FND amines and FND amides. Only the *in vitro* chromosome aberration assay for PEG-20 tallow amine and one Ames test were positive, among all of these chemicals.

Reproductive and developmental toxicity data are available for PEG-2 cocamine and PEG-15 tallow amine. No evidence of a teratogenic effect was observed in any of the studies. Reproductive toxicity studies of the analogs showed effects on reproductive performance at doses that were generally comparable to doses causing maternal toxicity.

An evaluation of representative PEG-4 cocamine structure using the TIMES® indicated that this ingredient has the potential to be a weak sensitizer, because of potential formation of hydroperoxides by autoxidation of the ethoxylate chains. This result was consistent with a report that ethoxylated alcohols were susceptible to autoxidation when exposed to air at ambient temperatures, in daylight for 18 months. Hydroperoxides were the primary oxidation products formed. No other alert for sensitization potential was noted in the PEGs cocamine structure.

DISCUSSION

This safety assessment includes a re-review of PEG-2, -3, -5, -10, -15, and -20 cocamine. In 1999, the Panel concluded that the data were insufficient to support the safety of these ingredients for use in cosmetics. In 2011 and 2012, the CIR SSC submitted requests to re-review these ingredients, along with new information and analyses to support a re-review. In addition, the PCPC recommended adding other, related ingredients to this ingredient family. In 2012, the Panel agreed that the additional information warranted re-opening the safety assessment of the 6 previously-reviewed PEGs cocamine ingredients, and to include 41 other ingredients to the safety assessment.

The Panel noted gaps in the available safety data for the PEGs cocamine and related ingredients in this safety assessment. However, the data available for some of these ingredients and their analogs, together with the SAR-based read-across analysis presented, can be used to support the safety of the 47 ingredients addressed in this report.

The Panel agreed that gaps in genotoxicity and systemic toxicity data can be filled for these ingredients by reading across from the genotoxicity and 28-day toxicity test data available, especially for PEG-2 tallow amine, and by applying the SAR-based framework to identify and evaluate analogs for read-across analyses. The selected analogs adequately covered the chemical space of these ingredients. The toxicology study summaries were sufficient to enable addressing all of the toxicology endpoints of potential concern for these ingredients in a safety assessment. Based on the toxicology data, the selected analogs showed sufficient concordance and consistency in biological responses (quantitative and qualitative) to support the read-across analysis. The read-across analysis was plausible and sufficiently persuasive to warrant a low or medium uncertainty rating.

Although no sensitization studies were found or submitted for PEG-2 cocamine, one negative test on PEG-2 oleamine and two studies on PEG-2 tallow amine addressed this endpoint. The studies on PEG-2 tallow amine included a negative test for delayed contact hypersensitivity in guinea pigs and an apparently positive LLNA in mice (EC3<0.1%). The Panel noted that the equivocal results of the LLNA for dermal sensitization of PEG-2 tallow amine were confounded by the irritant properties of the ingredient, and were inconsistent with the results of the guinea pig test. A QSAR analysis of a representative PEG-4 cocamine structure predicted that PEG-4 cocamine has the potential to be a weak sensitizer, because of potential formation of hydroperoxides by autoxidation of the ethoxylate chains. However, the Panel found that exposure durations and frequencies for the smaller ingredients in this group (i.e., PEG-2, 3, 4, and 5 cocamine and related ingredients) would be relatively low, because these ingredients are used predominantly in rinse-off hair-coloring products. Further, none of the reported use concentrations for leave-on or rinse-off products exceeds 4%. Thus, sensitization from the use of cosmetic products containing these ingredients is not a likely concern.

The Panel also noted that the tallow moieties of several of the selected analogs, including PEG-2 tallow amine, have greater degrees of unsaturation and, consequently, greater susceptibility to epoxidation than the fatty acid moieties of the PEGs cocamine and other related ingredients. Thus, the incorporation of the genotoxicity and repeated-dose toxicity data available for these analogs represents a conservative approach to the read-across analysis of the ingredient group.

The Panel stated that products containing the PEGs cocamine or related ingredients must be formulated to be non-irritating, because the potential exists for dermal irritation with the use of products containing these ingredients.

Additionally, the Panel noted that some or all of the fatty-acid moieties of these ingredients may be unsaturated or partially hydrogenated. The unsaturated fatty acid and trans-fatty acid moieties of these ingredients are subject to autoxidation, yielding hydroperoxides that are likely sensitizers. The Panel cautioned that products containing these ingredients should be formulated to minimize autoxidation and production of potentially allergenic hydroperoxides.

To ensure the absence of pathogenic agents in the ingredients, the PEGs tallow amine and PEGs hydrogenated tallow amine must be made from tallow containing no more than 0.15% insoluble impurities by weight.

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 limit these impurities in PEGs cocamine and related ingredients before blending them into cosmetic formulations.

Plants are the source of the fatty acids used to manufacture some of the ingredients of this report. These ingredients are not expected to contain residual pesticides or heavy metals because the production of the ingredients involves significant processing. However, the Expert Panel stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit these impurities in these ingredients before blending into cosmetic formulations.

The Panel noted reports that raw and dried copra (ie, dried coconut kernels from which the oil is obtained) can be contaminated with aflatoxin. The Panel believes PEGs cocamine ingredients manufactured using the fatty acids in coconut oil would not contain significant levels of aflatoxin; the Panel adopted the USDA designation of ≤ 15 ppb as corresponding to “negative” aflatoxin content.

PEGs cocamine and related ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

The Panel discussed the issue of incidental inhalation exposure from PEGs cocamine and related ingredients. These ingredients are reportedly used at concentrations up to 3% in cosmetic products that may be

aerosolized. There were no inhalation toxicity data available. However, the Panel noted that 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

The Panel also noted the absence of use concentration data for PEG-2 rapeseedamine, in particular, because this ingredient had the greatest use frequency (255) reported to the VCRP. In the absence of this data, the Panel assumed that the 2-rapeseedamine is used in hair coloring products at the same concentrations as PEG-2 oleamine (eg, 3.5% highest reported maximum concentration)

Generally, the Panel expressed support for developing the SAR-based framework as a systematic approach to identifying possible analogs for read-across assessments, and categorizing the analogues as suitable, suitable with interpretation, and suitable with precondition. However, the Panel emphasized the importance of developing quantitative measures for the key decision-making steps of the approach, characterizing the boundary conditions and assumptions of the models applied, and using actual test data for the class of chemicals to which the ingredients belong to validate computational predictions.

CONCLUSION

The Panel concluded that the following 47 PEGs cocamine and related ingredients are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating:

PEG-2 cocamine
PEG-3 cocamine*
PEG-4 cocamine*
PEG-5 cocamine
PEG-8 cocamine*
PEG-10 cocamine*
PEG-12 cocamine*
PEG-15 cocamine
PEG-20 cocamine*
PEG-2 hydrogenated tallow amine*
PEG-5 hydrogenated tallow amine
PEG-8 hydrogenated tallow amine
PEG-10 hydrogenated tallow amine*
PEG-15 hydrogenated tallow amine*
PEG-20 hydrogenated tallow amine*
PEG-30 hydrogenated tallow amine*
PEG-40 hydrogenated tallow amine*
PEG-50 hydrogenated tallow amine*
PEG-2 lauramine*
PEG-2 oleamine
PEG-5 oleamine*
PEG-6 oleamine*
PEG-10 oleamine*
PEG-15 oleamine*
PEG-20 oleamine*
PEG-25 oleamine*
PEG-30 oleamine*
PEG-12 palmitamine*
PEG-2 rapseedamine
PEG-2 soyamine
PEG-5 soyamine
PEG-8 soyamine*
PEG-10 soyamine*
PEG-15 soyamine*
PEG-2 stearamine*
PEG-5 stearamine*
PEG-10 stearamine*
PEG-15 stearamine*
PEG-50 stearamine*
PEG-2 tallow amine
PEG-7 tallow amine*
PEG-11 tallow amine*
PEG-15 tallow amine*
PEG-20 tallow amine*
PEG-22 tallow amine*
PEG-25 tallow amine*
PEG-30 tallow amine*

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

This conclusion supersedes the earlier conclusion issued by the Expert Panel for PEG-2, -3, -4, -5, -10, -15 and -20 cocamine in 1999.

TABLES

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

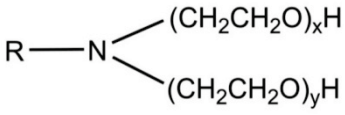
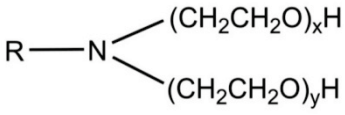
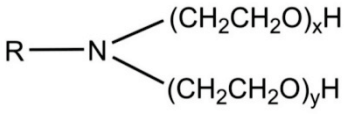
Ingredient CAS No.	Definition / Structure	
PEG-2 cocamine 61791-14-8 (generic)	PEG-2 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 2. [The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14. The structure of PEG-2 cocamine will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-3, -4, and -5 cocamine.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Emulsifying Agents
PEG-3 cocamine 61791-14-8 (generic)	PEG-3 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 3. [The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14. The structure of the smallest member of the group, PEG-2 cocamine, will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-3 cocamine.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Emulsifying Agents
PEG-4 cocamine 61791-14-8 (generic)	PEG-4 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 4. [The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14. The structure of the smallest member of the group, PEG-2 cocamine, will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-4 cocamine.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Cleansing Agents; Surfactants – Dispersing Agents; Surfactants – Emulsifying Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

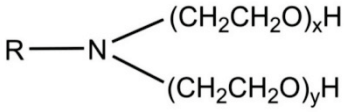
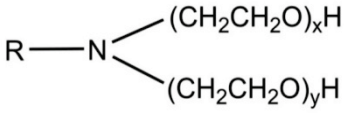
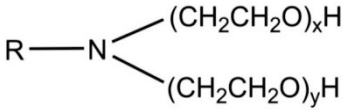
Ingredient CAS No.	Definition / Structure	
PEG-5 cocamine 61791-14-8 (generic)	PEG-5 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 5. [Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14. The structure of the smallest member of the group, PEG-2 cocamine, will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 cocamine.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Emulsifying Agents
PEG-8 cocamine 61791-14-8 (generic)	PEG-8 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 8. [The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Cleansing Agents; Surfactants – Dispersing Agents; Surfactants – Emulsifying Agents
PEG-10 cocamine 61791-14-8 (generic)	PEG-10 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 10. [The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Emulsifying Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

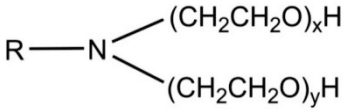
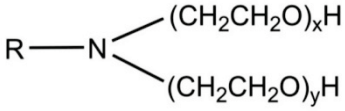
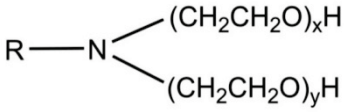
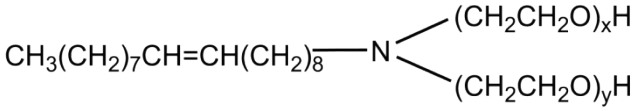
Ingredient CAS No.	Definition / Structure	
PEG-12 cocamine 61791-14-8 (generic)	PEG-12 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 12. [The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Cleansing Agents; Surfactants – Dispersing Agents; Surfactants – Emulsifying Agents
PEG-15 cocamine 61791-14-8 (generic)	PEG-15 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 15. [The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Emulsifying Agents
PEG2-20 cocamine 61791-14-8 (generic)	PEG-20 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene glycol groups has an average value of 20. [The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][14] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,45]	Surfactants – Emulsifying Agents; Surfactants – Solubilizing Agents
PEG-2 oleamine 26635-93-8 (generic)	PEG-2 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 2. [The structure of PEG-2 oleamine will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2.][14]	Surfactants – Emulsifying Agents; Surfactants – Foam Boosters

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

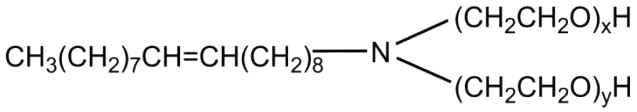
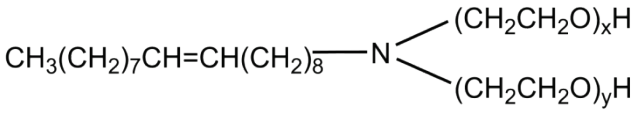
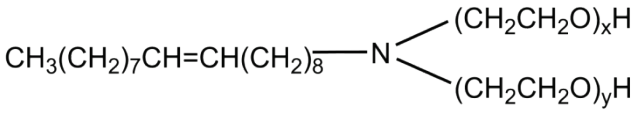
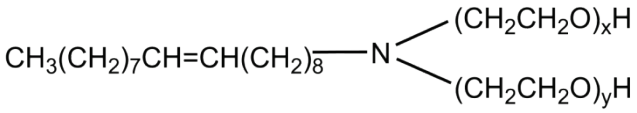
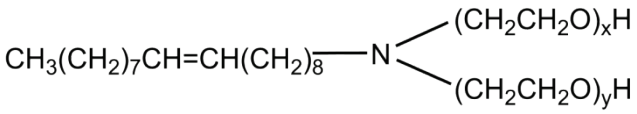
Ingredient CAS No.	Definition / Structure	
PEG-5 oleamine 26635-93-8 (generic)	PEG-5 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 5. [The structure of the smallest member of the group, PEG-2 oleamine, will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 oleamine.][14]	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-6 oleamine 26635-93-8 (generic)	PEG-6 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 6.	Surfactants – Emulsifying Agents; Surfactants – Foam Boosters
PEG-10 oleamine 26635-93-8 (generic)	PEG-10 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 10.	Not reported
PEG-15 oleamine 26635-93-8 (generic)	PEG-15 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 15.	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-20 oleamine 26635-93-8 (generic)	PEG-20 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 20.	Not reported

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

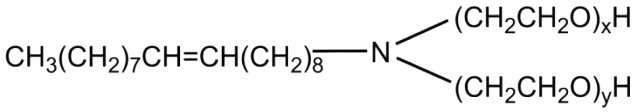
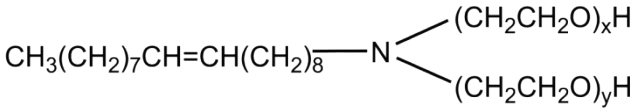
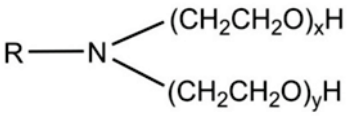
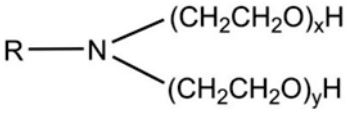
Ingredient CAS No.	Definition / Structure	
PEG-25 oleamine 26635-93-8 (generic)	PEG-25 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 25.	Not reported
PEG-30 oleamine 26635-93-8 (generic)	PEG-30 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 30.	Antistatic Agents; Surfactants – Cleansing Agents; Surfactants – Solubilizing Agents
PEG-2 tallow amine 61791-26-2 (generic)	PEG-2 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 2. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty-acid derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. The structure of PEG-2 tallow amine, will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2.][14] [The fatty chains in tallow vary from about 14 to 18 carbons long][4]	Antistatic Agents
PEG-7 tallow amine 61791-26-2 (generic)	PEG-7 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 7. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty-acid derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. [The fatty chains in tallow vary from about 14 to 18 carbons long][4]	Antistatic Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

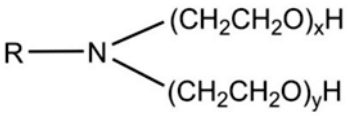
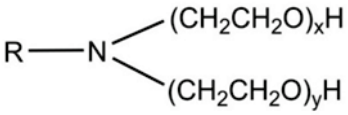
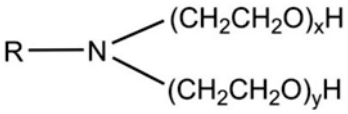
Ingredient CAS No.	Definition / Structure	
PEG-11 tallow amine 61791-26-2 (generic)	PEG-11 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 11. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty-acid derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. [The fatty chains in tallow vary from about 14 to 18 carbons long][4]	Antistatic Agents
PEG-15 tallow amine 61791-26-2 (generic)	PEG-15 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 15. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty-acid derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. [The fatty chains in tallow vary from about 14 to 18 carbons long][4]	Antistatic Agents
PEG-20 tallow amine 61791-26-2 (generic)	PEG-20 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 20. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty-acid derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. [The fatty chains in tallow vary from about 14 to 18 carbons long][4]	Antistatic Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

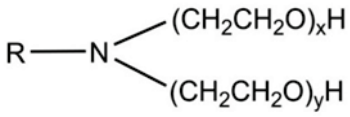
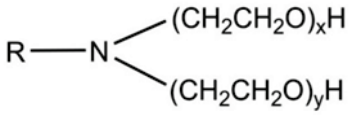
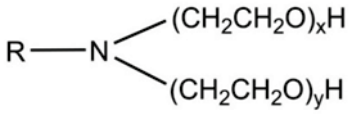
Ingredient CAS No.	Definition / Structure	
PEG-22 tallow amine 61791-26-2 (generic)	PEG-22 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 22. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty-acid derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. [The fatty chains in tallow vary from about 14 to 18 carbons long][4]	Hair Coloring Agents
PEG-25 tallow amine 61791-26-2 (generic)	PEG-25 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 25. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty-acid derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. [The fatty chains in tallow vary from about 14 to 18 carbons long][4]	Antistatic Agents
PEG-30 tallow amine 61791-26-2 (generic)	PEG-30 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 30. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty-acid derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. [The fatty chains in tallow vary from about 14 to 18 carbons long][4]	Hair Coloring Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

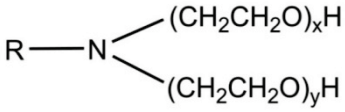
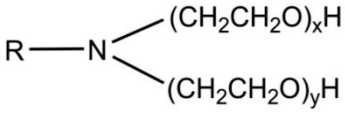
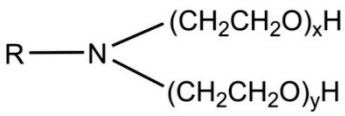
Ingredient CAS No.	Definition / Structure	
PEG-2 hydrogenated tallow amine 61791-26-2 (generic)	PEG-2 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 2. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. The structure of PEG-2 hydrogenated tallow amine will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 hydrogenated tallow amine. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents; Surfactants – Foam Boosters
PEG-5 hydrogenated tallow amine 61791-26-2 (generic)	PEG-5 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 5. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. The structure of the smallest member of the group, PEG-2 hydrogenated tallow amine, will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 hydrogenated tallow amine. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents
PEG-8 hydrogenated tallow amine 61791-26-2 (generic)	PEG-8 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 8. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents, Surfactants – Emulsifying Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

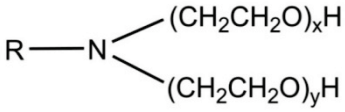
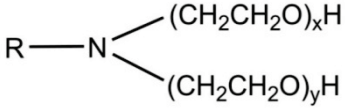
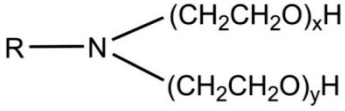
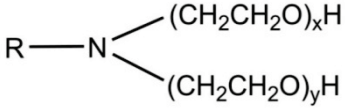
Ingredient CAS No.	Definition / Structure	
PEG-10 hydrogenated tallow amine 61791-26-2 (generic)	PEG-10 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 10. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-15 hydrogenated tallow amine 61791-26-2 (generic)	PEG-15 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 15. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-20 hydrogenated tallow amine 61791-26-2 (generic)	PEG-20 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 20. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents; Surfactants – Emulsifying Agents; Surfactants – Solubilizing Agents
PEG-30 hydrogenated tallow amine 61791-26-2 (generic)	PEG-30 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 30. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents; Surfactants – Solubilizing Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

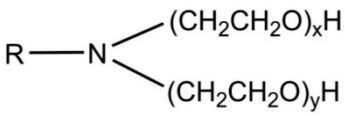
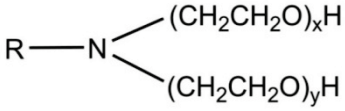
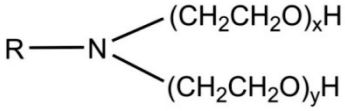
Ingredient CAS No.	Definition / Structure	
PEG-40 hydrogenated tallow amine 61791-26-2 (generic)	PEG-40 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 40. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents; Surfactants – Solubilizing Agents
PEG-50 hydrogenated tallow amine 61791-26-2 (generic)	PEG-50 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x+y has an average value of 50. [In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.][14] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][12,13,46]	Antistatic Agents; Surfactants – Solubilizing Agents
PEG-2 soyamine 61791-24-0 (generic)	PEG-2 soyamine is a series of polyethylene glycol derivatives of soy acid that conform generally to the formula:  shown above, where R represents the alkyl groups derived from the fatty acids of soy and x+y has an average value of 2. [The structure of PEG-2 soyamine will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2..][14] [The fatty chains in soy oil are predominantly 18 carbons long][15]	Antistatic Agents; Surfactants – Foam Boosters

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

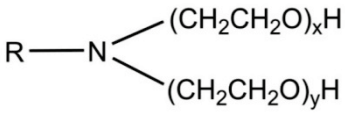
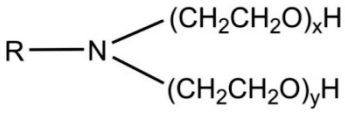
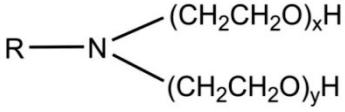
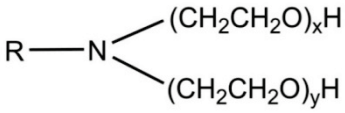
Ingredient CAS No.	Definition / Structure	
PEG-5 soyamine 61791-24-0 (generic)	PEG-5 soyamine is a series of polyethylene glycol derivatives of soy acid that conform generally to the formula:  shown above, where R represents the alkyl groups derived from the fatty acids of soy and x+y has an average value of 5. [The structure of the smallest member of the group, PEG-2 soyamine, will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 soyamine.][14] [The fatty chains in soy oil are predominantly 18 carbons long][15]	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-8 soyamine 61791-24-0 (generic)	PEG-8 soyamine is a series of polyethylene glycol derivatives of soy acid that conform generally to the formula:  shown above, where R represents the alkyl groups derived from the fatty acids of soy and x+y has an average value of 8. [The fatty chains in soy oil are predominantly 18 carbons long][15]	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-10 soyamine 61791-24-0 (generic)	PEG-10 soyamine is a series of polyethylene glycol derivatives of soy acid that conform generally to the formula:  shown above, where R represents the alkyl groups derived from the fatty acids of soy and x+y has an average value of 10. [The fatty chains in soy oil are predominantly 18 carbons long][15]	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-15 soyamine 61791-24-0 (generic)	PEG-15 soyamine is a series of polyethylene glycol derivatives of soy acid that conform generally to the formula:  shown above, where R represents the alkyl groups derived from the fatty acids of soy and x+y has an average value of 15. [The fatty chains in soy oil are predominantly 18 carbons long][15]	Antistatic Agents; Surfactants – Emulsifying Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

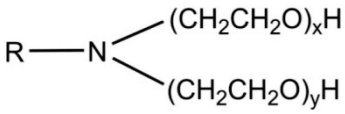
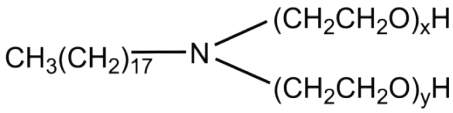
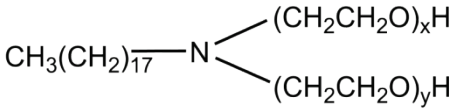
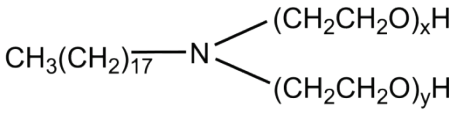
Ingredient CAS No.	Definition / Structure	
PEG-2 rapeseedamine no CAS# provided	PEG-2 rapeseedamine is the polyethylene glycol derivative of rapeseedamine that conforms generally to the formula:  where R represents the alkyl group derived from the fatty acids of rapeseed oil and x+y has an average value of 2. [The structure of PEG-2 rapeseedamine will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2.][14] [The fatty chains in rapeseed oil are predominantly 16 to 22 carbons long][15,45]	Antistatic Agents
PEG-2 stearamine 9003-93-4 (generic)	PEG-2 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x+y has an average value of 2. [The structure of PEG-2 stearamine will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2.][14]	Antistatic Agents; Surfactants – Foam Boosters
PEG-5 stearamine 9003-93-4 (generic)	PEG-5 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x+y has an average value of 5. [The structure of the smallest member of the group, PEG-2 stearamine, will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 stearamine.][14]	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-10 stearamine 9003-93-4 (generic)	PEG-10 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x+y has an average value of 10.	Antistatic Agents; Surfactants – Emulsifying Agents

Table 1. Definitions and idealized structures of the ingredients in this safety assessment.[1]

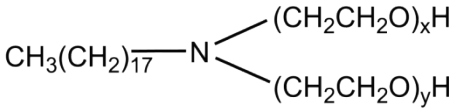
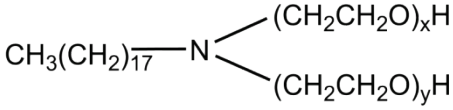
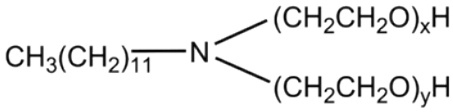
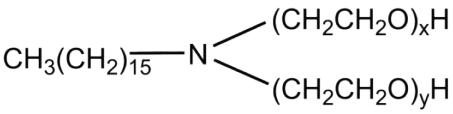
Ingredient CAS No.	Definition / Structure	
PEG-15 stearamine 9003-93-4 (generic)	PEG-15 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x+y has an average value of 15.	Antistatic Agents; Surfactants – Emulsifying Agents
PEG-50 stearamine 9003-93-4 (generic)	PEG-50 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x+y has an average value of 50.	Antistatic Agents; Surfactants – Solubilizing Agents
PEG-2 lauramine no CAS# provided	PEG-2 lauramine is the polyethylene glycol derivative of lauryl amine that conforms to the formula:  where the alkyl group is derived from lauric acid (C12) and x+y has an average value of 2. [The structure of PEG-2 lauramine will have two *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x=0 and y=2.][14]	Antistatic Agents; Surfactants – Foam Boosters
PEG-12 palmitamine 68155-33-9, generic	PEG-12 palmitamine is the polyethylene glycol derivative of palmitamine that conforms to the formula:  where the alkyl group is derived from palmitic acid (Cl6) and x+y of the polyethylene glycol groups has an average value of 12. [The fatty chains in palm oil vary from about 8 to 18 carbons long][45]	Antistatic Agents; Surfactants – Emulsifying Agents

Table 2. Previously-reviewed ingredients of potential relevance

Ingredient(s)	Conclusion (year issued; highest reported maximum use concentration)	Reference
Triethylene glycol and polyethylene glycols (PEGs)-4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEGs ≥ 4	Safe as used (1993, 2006 & 2010; 85% in leave-ons; 67% in rinse-offs)	16,47,48
Lauramine & stearamine	Use not supported* (1995; No use concentrations or frequencies reported)	49
Cocos nucifera (coconut) oil and related ingredients, including: Ammonium cocomonoglyceride sulfate Butylene glycol cocoate Caprylic/capric/coco glycerides Cecyl cocoate Cocoglycerides Coconut acid Coconut alcohol Coconut oil decyl esters Ethylhexyl cocoate Hydrogenated coco-glycerides Hydrogenated coconut acid Hydrogenated coconut oil Isodecyl cocoate Lauryl cocoate Magnesium cocoate Methyl cocoate Octyldodecyl cocoate Pentaerythrityl cocoate Potassium cocoate Potassium hydrogenated cocoate Sodium cocoate Sodium cocomonoglyceride sulfate Sodium hydrogenated cocoate Tridecyl cocoate	Safe as used (1986; reaffirmed with additional ingredients 2011; 80% in leave-ons; 52% in rinse-off)	50,51
Plant-derived fatty acid oils, including: Brassica campestris (rapeseed) oil unsaponifiables Brassica campestris (rapeseed) seed oil Brassica napus seed oil Coconut acid Cocos nucifera (coconut) oil Cocos nucifera (coconut) seed butter Glycine soja (soybean) oil Glycine soja (soybean) oil unsaponifiables Hydrogenated coconut acid	Safe as used (2011; 100% in leave-ons; 95% in rinse-offs)	45

(*continued* on *next page*)

Table 2. Previously-reviewed ingredients of potential relevance

Ingredient(s)	Conclusion (year issued; highest reported maximum use concentration)	Reference
Plant-derived fatty acid oils, including: (*continued from previous page*) Hydrogenated coconut oil Hydrogenated palm acid Hydrogenated palm kernel oil Hydrogenated palm oil Hydrogenated rapeseed oil Hydrogenated soybean oil Magnesium cocoate Palm acid Palm kernel acid Potassium cocoate Potassium hydrogenated cocoate Potassium hydrogenated palmate Potassium palm kernelate Potassium palmate Potassium rapeseedate Potassium soyate Rapeseed acid Sodium cocoa butterate Sodium cocoate Sodium hydrogenated cocoate Sodium hydrogenated palmate Sodium palm kernelate Sodium palmate Sodium rapeseedate Sodium soyate Soy acid *Others*		
Oleic acid, lauric acid, palmitic acid, myristic acid and stearic acid	Safe as used (1987; reaffirmed 2006; 22% in leave-ons; 43% in rinse-offs)	[52,53]
Tallow, tallow glyceride, tallow glycerides, hydrogenated tallow glyceride, and hydrogenated tallow glycerides	Safe as used (1990, reaffirmed 2008; 14% in leave-ons; 78% in rinse-offs)	[54,55]

Table 3. Supplier specifications and analytical data for PEGs cocamine and related ingredients

Property	Value	Ref.
PEG-2 Cocamine		
Physical Appearance @ 25 ºC	Yellow to amber liquid / Clear liquid	[5] / [17]
Color, (Gardner scale)	2.0 max. / 11.0 max.	[5] / [17]
Refractive Index @ 25 ºC	~1.466	[17]
pH (10% in IPA/H_2O)	9.0 to11.0	[5]
Amine Value	185 to 200	[17]
Secondary Amine (%)	0.5 max.	[19]
Primary & Secondary Amine (%)	5.0 max.	[17]
Tertiary Amine (%)	97.0 min. / 95.0 max. / 95 min. / 97 to 100	[5] / [17] / [56] / [19]
Nitrosamine (ppb)	50 max.	[19]
Moisture (%)	0.5 max. / 1.0 max. / Residual	[5] / [17] / [19]
Neutralization Eq.	290 to 310 / 280 to 303	[5] / [17]
PEG-5 Cocamine		
Physical Appearance	Yellow to amber liquid / Liquid @ 25ºC	[57] / [58]
Color, Gardner	12.0 max. / 7 max.	[57] / [58]
Specific Gravity @ 25ºC	0.976	[58]
Viscosity (kg/[s x m]) @ 20ºC	0.15	[58]
Vapor Pressure (mmHg) @ 20ºC	<0.1	[58]
Melting Point (ºC)	-9	[58]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[58]
pH (5% soln.)	9.0 to 11.0	[57]
Amine Value	128 to 138 / 129 to 137	[57] / [58]
Secondary Amine (%)	0.5 max.	[19]
Primary & Secondary Amine (%)	2 max.	[58]
Tertiary Amine (%)	96 min. / 95 min. / 97 to 100	[57] / [56] / [19]
Nitrosamine (ppb)	50 max.	[19]
Moisture (%)	1.0 max. / Residual / 1 max.	[57] / [19] / [58]
Neutralization Eq.	406 to 439 / 410 to 435	[57] / [58]
PEG-15 Cocamine		
Physical Appearance	Yellow to amber liquid	[5,59]
Color, Gardner	9.0 max. / 12 max.	[5] / [59]
pH (10% in IPA/H_2O / 5% soln.)	9.0 to 11.0 / 9 to 10.5	[5] / [59]
Amine Value	62 to 68	[59]
Tertiary Amine (%)	96 min.	[5,59]

Table 3. Supplier specifications and analytical data for PEGs cocamine and related ingredients

Moisture (%)	1.0 max.	[5,59]
Neutralization Eq.	825 to 905	[5,59]
PEG-2 Tallow Amine		
Physical Appearance	Liquid to semi-solid (paste) / Pale brown-yellow liquid / Paste @ 25ºC	[60] / [13,46] / [61]
Color, Gardner	8 max. / 6 max.	[60] / [61]
Average Molecular Weight (g/mol)	344 / 343	[13,46]/ [12]
Specific Gravity @ 25ºC	0.916	[61]
Viscosity (kg/[s x m]) @ 50ºC	0.034	[61]
Vapor Pressure (mm Hg) @ 20ºC	<0.1	[61]
Melting Point (ºC)	29	[61]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[61]
Amine Value	156 to 165	[61]
Primary Amine (%)	0.4 / 0.8	[46] / [12]
Secondary Amine (%)	0.7 / 0.7	[46] / [12]
Primary & Secondary Amine (%)	1.2 / 1.5 / 3 max.	[13,46] / [12] / [61]
Tertiary Amine (%)	97.0 min. / 98.6 / 98.5 / 96	[60] / [13,46] / [12] / [61]
Chain Length Distributions (%)	C12E2: 1.5 / 0.3 C14E2: 3.0 / 1.6 C15E2: 1.0 / 4.4 C16E2: 0.2 / 0.5 C16E2: 34.2 / 29.9 C17E2: 1.9 / 1.5 C18E2: 2.2 / 2.3 C18E2: 51.7 / 54.4 C16E3: 1.4 / 0.9 C18E3: 2.2 / 1.2 C20E2: 0.7 / 2.0 Unknown: Not reported / 1	[13,46] / [12]
Moisture (%)	1.0 max.	[60]
Neutralization Eq.	350 to 370 / 340 to 360	[60] / [61]
PEG-5 Tallow Amine		
Physical Appearance	Clear liquid / Liquid-paste at 25ºC	[62] / [63]
Color, Gardner	8 max. / 7 max.	[62] / [63]
Specific Gravity @ 25ºC	0.950	[64]
Vapor Pressure (mmHg) @ 20ºC	<0.1	[64]
Melting Point (ºC)	12	[64]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[64]
pH (10% in IPA/H_2O)	9 to 11 / 11 to 11.6	[62] / [63]
Solubility (5% @ 20ºC)	Water, acetone, isopropanol, propylene glycol, xylene, ethanol	[64,65]
Amine Value	113 to 119	[64]
Primary & Secondary Amine (%)	2 max.	[64]
Tertiary Amine (%)	97 min. / 95 min. / 98 min.	[62] / [56] / [63]
Moisture (%)	1 max. / 1 max.	[62] / [63]

Table 3. Supplier specifications and analytical data for PEGs cocamine and related ingredients

Neutralization Eq.	475 to 495 / 470 to 495	[62] / [63]
PEG-15 Tallow Amine		
Physical Appearance	Clear liquid / Liquid-paste at 25ºC	[66] / [67]
Color, Gardner	8 max. / 8 max.	[66] / [67]
Specific Gravity @ 25ºC	1.024	[67]
Vapor Pressure (mmHg) @ 20ºC	<0.1	[67]
Melting Point (ºC)	-3	[67]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[67]
pH (5% soln.)	9 to 10.5 / 11 to 11.6	[66] / [67]
Solubility @ 25ºC	Water, acetone, isopropanol	[67]
Amine Value	59 to 63 / 59 to 63	[66] / [67]
Primary & Secondary Amine (%)	1 max.	[67]
Tertiary Amine (%)	97 min.	[66]
Moisture (%)	1.0 max. / 1 max.	[66] / [67]
Neutralization Eq.	890 to 951 / 890 to 950	[66] / [67]
PEG-2 Hydrogenated Tallow Amine		
Physical Appearance	Solid @ 25ºC	[68]
Color, Hazen	300 max.	[68]
Solubility @ 20ºC	Water, ethanol, propylene glycol	[68]
Density (kg/m^3) @ 50ºC	880	[68]
Viscosity (kg/[s x m]) @ 50ºC	0.042	[68]
Activity (%)	100	[68]
Tertiary Amine (%)	95 min. / 97 min.	[56] / [68]
Moisture (%)	1.0 max.	[68]
Neutralization Eq.	338 to 360	[68]
PEG-8 Hydrogenated Tallow Amine		
Physical Appearance	Amber Viscous Liquid (200 ºC)	[5]
Solubility in water at 20°C	0.4%; dispersion at > 0.4%	[5]
Specific Gravity @ 200 ºC	1.027±0.050	[5]
Activity (%)	93 min.	[5]
Ash (%)	0.05 max.	[5]
Iron (ppm)	20 max.	[5]
Heavy Metals (ppm)	5 max.	[5]

Table 3. Supplier specifications and analytical data for PEGs cocamine and related ingredients

PEG-5 Oleamine		
Solubility	Water soluble	[5]
Specific Gravity @ 25 ºC	0.94	[5]
PEG-15 Oleamine		
Solubility	Water soluble	[5]
Specific Gravity @ 25 ºC	1.01	[5]
PEG-5 Soyamine		
Physical Appearance	Clear liquid at 25ºC	[69]
Color (Gardner)	10 max.	[69]
Specific Gravity @ 25ºC	0.952	[69]
Vapor Pressure (mmHg) @ 20ºC	<1	[69]
Melting Point (ºC)	6	[69]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[69]
Amine Value (mgKOH/g)	113 to 119	[69]
Primary & Secondary Amine (%)	3 max.	[69]
Moisture (%)	1 max.	[69]
Neutralization Eq.	470 to 495	[69]
PEG-15 Soyamine		
Physical Appearance	Clear liquid at 25ºC	[70]
Color (Gardner)	10 max.	[70]
Specific Gravity @ 25ºC	1.023	[70]
Melting Point (ºC)	-8	[70]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[70]
pH	11.5	[70]
Amine Value	59 to 63	[70]
Primary & Secondary Amine (%)	1 max.	[70]
Moisture (%)	1 max.	[70]
Neutralization Eq.	895 to 955	[70]
PEG-5 Stearamine		
Physical Appearance @ 25 ºC	Yellow soft solid / Solid @ 25ºC	[71] / [72]
Color, (Gardner scale)	9 max. / 5 max.	[71] / [72]
Specific Gravity @ 60ºC	0.876	[72]
Viscosity (kg/[s x m]) @ 50ºC	0.068	[72]

Table 3. Supplier specifications and analytical data for PEGs cocamine and related ingredients

Vapor Pressure (mmHg) @ 25ºC	<0.1	[72]
Melting Point (ºC)	50	[72]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[72]
pH (5% soln.)	9.0 to10.0	[71]
Hydroxyl Number	210 to 240	[71]
Amine Value	110 to 120 / 150 to 160	[71] / [72]
Primary & Secondary Amine (%)	3 max.	[72]
Tertiary Amine (%)	97 min. / 95 min. / 97 min.	[71] / [56] / [72]
Moisture (%)	1.0 max.	[71] / [72]
Neutralization Eq.	470 to 510	[71]
PEG-10 Stearamine		
Solubility	Water soluble	[5]
Specific Gravity at 25 ºC	0.98	[5]
PEG-15 Stearamine		
Physical Appearance @ 25 ºC	Liquid-paste @ 25ºC	[73]
Color, (Gardner scale)	8 max.	[73]
Specific Gravity @ 50ºC	1.015	[73]
Vapor Pressure (mmHg) @ 20ºC	<0.1	[73]
Melting Point (ºC)	9	[73]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[73]
pH	11 to 11.6	[73]
Amine Value	58 to 62	[73]
Primary & Secondary Amine (%)	1 max.	[73]
Moisture (%)	1 max.	[73]
Neutralization Eq.	900 to 960	[73]

Table 4. Chain length distribution and degree of unsaturation of the fatty acids in coconut oil[45]

Fatty Acids	Fatty Acid Chain Length	Degree of Unsaturation	Composition
Caproic	C6	None	0% to 1%
Caprylic	C8	None	5% to 9%
Capric	C10	None	5% to 10%
Lauric	C12	None	44% to 53%
Myristic	C14	None	13% to 19%
Palmitic	C16	None	8% to 11%
Stearic	C18	None	1% to 3%
Palmitoleic	C16	1	0% to 1%
Oleic	C18	1	5% to 8%
Linoleic	C18	2	1% to 3%

Table 5. Chain length distribution and degree of unsaturation of the fatty acids in tallow[4]

Fatty Acid Chain Length	**Degree of Unsaturation**	**Composition**
C14	None	0% to 6%
C16	None	20% to 37%
C18	None	14% to 21%
C16	1	3% to 9%
C18	1	35% to 46%
C18	2	4% to 10%
C18	3	0% to 3%

Table 6. Chain length distribution and degree of unsaturation of the fatty acids in rapeseed oil[15,45]

Fatty Acids	Fatty Acid Chain Length	Degree of Unsaturation	Composition
Palmitic	C16	None	1.5% to 4.5%
Stearic	C18	None	0.7% to 1.5%
Oleic	C18	1	12.1% to 61.7%
Linoleic	C18	2	11.4% to 22.1%
Linolenic	C18	3	8.3% to 12.5%
Eicosenioc	C20	1	5.6% to 10.9%
Erucic	C22	1	0.2% to 58.6%

Table 7. Chain length distribution and degree of unsaturation of the fatty acids in soybean oil[15]

Fatty Acids	Fatty Acid Chain Length	Degree of Unsaturation	Composition
Oleic	C18	1	11.5% to 60%
Linoleic	C18	2	25% to 63.1%
Linolenic	C18	3	2.9% to 12.1%

Table 8. Frequency (2015) and concentration of use (2014) according to duration and type of exposure for PEGs-Cocamine ingredients. [20,21,74]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	PEG-5 Hydrogenated Tallow Amine		**PEG-8 Hydrogenated Tallow Amine**		**PEG-2 Oleamine**		**PEG-2 Rapeseedamine**	
Totals†	**1**	**NR**	**4**	**NR**	**254**	**0.1-3.5**	**255**	**NR**
Duration of Use								
Leave-On	NR	NR	NR	NR	NR	0.16	NR	NR
Rinse Off	1	NR	4	NR	239	0.1-3.5	255	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	NR	NR	NR	0.16	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	1	NR	4	NR	254	0.1-3.5	255	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

	PEG-2 Soyamine		**PEG-5 Soyamine**		**PEG-2 Tallow Amine**	
Totals†	**39**	**NR**	**6**	**4**	**30**	**NR**
Duration of Use						
Leave-On	NR	NR	NR	NR	NR	NR
Rinse Off	39	NR	6	4	30	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	39	NR	6	4	30	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

NR = Not reported.

† 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.

Table 9. Current and historical frequency and concentration of use of PEGs cocamine according to duration and exposure.[2,20,21,74]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2015	**1996**	**2014**	**1995**	**2015**	**1996**	**2014**	**1995**
	PEG-2 Cocamine				**PEG-3 Cocamine**			
Totals†	**107**	**15**	**0.33**	**NR***	**NR**	**14**	**NR**	**NR***
Duration of Use								
Leave-On	NR	NR	0.33	NR	NR	NR	NR	NR
Rinse-Off	107	15	NR	NR	NR	14	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
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	0.33	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	0.33	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	107	15	NR	NR	NR	14	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

	2015	**1996**	**2014**	**1995**	**2015**	**1996**	**2014**	**1995**
	PEG-5 Cocamine				**PEG-15 Cocamine**			
Totals†	**1**	**NR**	**NR**	**NR***	**4**	**25**	**3**	**0.8-1.3**
Duration of Use								
Leave-On	NR	NR	NR	NR	4	20	3	0.8-1.3
Rinse-Off	1	NR	NR	NR	NR	5	NR	0.8-1
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	1.3
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	1[a]; 2[b]	3; 13[a]; 2[b]	3	1.0; 0.8[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	2[b]	1; 2[b]	NR	NR
Dermal Contact	NR	NR	NR	NR	3	19	3	1-1.3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	1	6	NR	0.8-1
Hair-Coloring	1	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	2	NR	1
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 9. Current and historical frequency and concentration of use of PEGs cocamine according to duration and exposure.[2,20,21,74]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2015	**1996**	**2014**	**1995**				
	PEG-20 Cocamine							
Totals†	**NR**	**38**	**NR**	**NR***				
Leave-On	NR	NR	NR	NR				
Rinse-Off	NR	37	NR	NR				
Diluted for (Bath) Use	NR	1	NR	NR				
Eye Area	NR	NR	NR	NR				
Incidental Ingestion	NR	NR	NR	NR				
Incidental Inhalation-Spray	NR	NR	NR	NR				
Incidental Inhalation-Powder	NR	NR	NR	NR				
Dermal Contact	NR	1	NR	NR				
Deodorant (underarm)	NR	NR	NR	NR				
Hair - Non-Coloring	NR	2	NR	NR				
Hair-Coloring	NR	35	NR	NR				
Nail	NR	NR	NR	NR				
Mucous Membrane	NR	1	NR	NR				
Baby Products	NR	NR	NR	NR				

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

NR – no reported use

*Unspecified PEGs cocamine ingredient was reported to have a concentration of 8%-20% in hair coloring products.

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

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

Table 10. Ingredients that are not reported to be in use.

PEG-3 Cocamine	PEG-25 Oleamine
PEG-4 Cocamine	PEG-30 Oleamine
PEG-8 Cocamine	PEG-12 Palmitamine
PEG-10 Cocamine	PEG-8 Soyamine
PEG-12 Cocamine	PEG-10 Soyamine
PEG-20 Cocamine	PEG-15 Soyamine
PEG-2 Hydrogenated Tallow Amine	PEG-2 Stearamine
PEG-10 Hydrogenated Tallow Amine	PEG-5 Stearamine
PEG-15 Hydrogenated Tallow Amine	PEG-10 Stearamine
PEG-20 Hydrogenated Tallow Amine	PEG-15 Stearamine
PEG-30 Hydrogenated Tallow Amine	PEG-50 Stearamine
PEG-40 Hydrogenated Tallow Amine	PEG-7 Tallow Amine
PEG-50 Hydrogenated Tallow Amine	PEG-11 Tallow Amine
PEG-2 Lauramine	PEG-15 Tallow Amine
PEG-5 Oleamine	PEG-20 Tallow Amine
PEG-6 Oleamine	PEG-22 Tallow Amine
PEG-10 Oleamine	PEG-25 Tallow Amine
PEG-15 Oleamine	PEG-30 Tallow Amine
PEG-20 Oleamine	

Table 11. Genotoxicity studies

Test Substance	Concentration/Dose (vehicle)	Method	Results	Reference
		IN VITRO		
PEG-2 tallow amine	up to 0.08 µl/plate with & without metabolic activation (ethanol)	Ames test on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, & TA1538; Positive controls: 2-nitrofluorene, 1,2-propane sultone, & 9- aminoacridine	Not mutagenic	4,5,9
PEG-8 stearamine	0.0008 to 0.08 µl/plate with & without metabolic activation (water)	Ames test on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, & TA1538; Positive controls: 2-nitrofluorene, 1,2-propane sultone, & 9- aminoacridine	Not mutagenic	*9,11,29*
PEG-15 tallow amine	up to 300 µg/plate without metabolic activation; up to 1000 µg/plate with metabolic activation (not specified)	Ames test on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, & TA1538; Positive controls not specified	Not mutagenic	*10*
PEG-20 tallow amine	up to 0.08 µl/plate with & without metabolic activation (water)	Ames test on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, & TA1538; Positive controls: 2-nitrofluorene, 1,2-propane sultone, & 9- aminoacridine	Not mutagenic	4,5,9
PEG-20 tallow amine (purity 99.5%)	0.33, 1.0, 3.3, 10, 33 & 100 µg/plate with & without metabolic activation (ethanol)	Mouse lymphoma mutation assay on $TK^{+/-}$ L5178Y cells; Positive controls not specified	Not mutagenic	4,5,9
PEG-20 tallow amine	Up to 0.03 µl/ml without metabolic activation & up to 0.3 µl/ml with metabolic activation	Cell chromosome aberrations test on Chinese hamster ovary (CHO) cells; Positive controls: triethylenemelamine (TEM) & cyclophosphamide (CP)	Increased numbers of aberrations appeared to be elevated without metabolic activation, but no concentration-response relationship detected Concentration-dependent increase in numbers of chromosome aberrations with metabolic activation	4,5,9
PEG-20 tallow amine	0.008×10^{-4} to 0.23×10^{-4} µl/ml (ethanol)	Unscheduled DNA synthesis (UDS) test on freshly prepared primary rat hepatocytes; Positive control: 7,12-dimethylbenz[a]anthracene (DMBA) dissolved in dimethyl sulfoxide (DMSO)	Not mutagenic	4,5,9
		IN VIVO		
PEG-2 tallow amine	10,860 mg/kg by gavage (distilled water)	Mouse micronucleus (MN) assay (performed in accordance with OECD methods & guidelines) on groups of 30 mice (15 of each sex/group) given a single dose of PEG-2 tallow amine; two additional groups of 30 mice (15 of each sex/group) served as controls; Positive control: One of the control groups received mitomycin C by intraperitoneal (ip) injection	Statistically-significant increase in number of micronucleated polychromatic erythrocytes 24 hours, but not 48 or 72 hours, after exposure to PEG-2 tallow amine, not considered treatment related because well within the ranges of historical controls; Ratio of polychromatic to normochromatic erythrocytes statistically-significantly reduced 24, 48 & 72 hours after exposure, suggesting treatment-related toxicity to bone marrow cells Clinical signs 72 hours after exposure: slight pallor of the extremities, diarrhea, slight-to-moderate piloerection, lethargy, decreased respiratory rate and ptosis, walking on toes, and greasy fur; One male animal died about 30 hours after treatment	4,5,9
PEG-15 tallow amine	100 mg/kg (not specified)	Mammalian MN assay (species tested not specified)	Not mutagenic	10

Table 11. Genotoxicity studies

Test Substance	Concentration/Dose (vehicle)	Method	Results	Reference
PEG-20 tallow amine	39, 130, or 390 mg/kg/day by gavage for 5 consecutive days (distilled water)	Cytogenicity study on groups of 10 Sprague-Dawley rats (5 of each sex/group) given PEG-20 tallow amine by gavage for 5 consecutive days; Two additional groups of 10 rats (5 of each sex/group) served as controls; Positive control: one control group received methylmethane sulfonate (MMS) by gavage	Not mutagenic All animals exposed to 390 mg/kg/day & 2 females exposed to the lower dose rates developed diarrhea; Some treated animals exhibited red-brownish exudates around the eyes & mouth, but this was not considered to be treatment related.	[4,5,9]

Table 12. Analog Group 1: PEG-2 Cocamine as a Structure of Interest (SOI)

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-Dose Toxicity	Developmental & Reproductive Toxicity (DART)	Ref.
SOI							
PEG-2 cocamine	61791-31-9	8-16	2	No data	No data (other than DART screening data)	Rat DART Screen: 2, 8, 23, 134 mg/kg/day (males) or 3, 9, 26, 148 mg/kg/day (females) via diet for 69-72 days. Developmental NOAEL = 23 mg/kg/day. Decreased postnatal survival, live litter size, # of pups born, & implantation sites. Reproductive NOAEL = 134 mg/kg/day (highest dose tested). Parental NOAEL = 23 mg/kg/day.	10
Analogs							
PEG-2 tallow amine	61791-44-4	14-18	2	Ames test: (-) *In vivo* mouse micronucleus test: (-)	Rat 90-Day Oral Study. 15, 50 or 150 mg/kg/day via diet; NOEL = 50 mg/kg/day. Palatability of diet decreased at high dose. Gross macroscopic observations: yellow coloration & thickening of mucosa in small intestine & regional mesenteric lymph nodes at high dose; histiocytosis in small intestine & mesenteric lymph nodes at mid & high dose. Rat 90-Day Oral Study. 0.8, 12 or 400 mg/kg/day via diet; NOEL = 12 mg/kg/day (based on body-weight gain) or 40 mg/kg/day (based on histiocytosis). Food consumption in all treated groups similar to control. Small decrease in body-weight gain in mid-dose males & high dose males & females; histiocytosis in small intestine & mesenteric lymph nodes at high dose. Dog 90-Day Oral Study. 13, 40 or 120 mg/kg/day via diet; NOEL = 13 mg/kg/day. Palatability issues at mid & high dose. GI clinical signs at mid & high dose (vomiting); histiocytosis in small intestine & regional lymph nodes at mid & high dose. Rabbit 28-Day Percutaneous Study. 0.1% or 0.5% aqueous dispersion (2 or 10 mg/kg/day), 5 days/week for 4 weeks. Slight-to-moderate skin irritation at both concentrations; no evidence of systemic toxicity.	No data	9,12,13

Table 12. Analog Group 1: PEG-2 Cocamine as a Structure of Interest (SOI)

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-Dose Toxicity	Developmental & Reproductive Toxicity (DART)	Ref.
PEG-2 C13-C15 alkyl amine	70955-14-5	13-15	2	No data	Rat 90-Day Oral Study. 15, 30 or 150 mg/kg/day via gavage; NOAEL = 15 mg/kg/day. Macro & microscopic changes in non-glandular stomach. Dog 90-Day Oral Study. 15, 30 or 100 mg/kg/day via capsule; NOAEL = 30 mg/kg/day. GI clinical signs: Increased alanine aminotransferase (ALT) females only; increased pigment accumulation in Kupffer cells & bile canaliculi females only.		10
PEG-4 cocamine	61791-14-8	8-16	4	No data	No data	No data	-

Table 13. Analog Group 2: PEG-4 Cocamine as a Structure of Interest (SOI)

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-dose Toxicity	Developmental & Reproductive Toxicity (DART)	Ref.
SOI							
PEG-4 cocamine	61791-14-8	8-16	4	No data	No data	No data	-
Analogs							
PEG-2 cocamine	61791-31-9	8-16	2	No data	No data	Rat DART Screen: 2, 8, 23, 134 mg/kg/day (M) or 3, 9, 26, 148 mg/kg/day (F) via diet for 69-72 days via diet; Developmental NOAEL 23 mg/kg/day; decreased postnatal survival, live litter size, # of pups born, implantation sites; Reproductive NOAEL 134 mg/kg/day (highest dose tested); Parental NOAEL 23 mg/kg/day	10
PEG-2 tallow amine	61791-44-4	16-18	2	Ames test: (-) *In vivo* mouse micronucleus test: (-)	Rat 90-Day Oral Study. 15, 50 or 150 mg/kg/day via diet; NOEL = 50 mg/kg/day. Palatability of diet decreased at high dose. Gross macroscopic observations: yellow coloration & thickening of mucosa in small intestine & regional mesenteric lymph nodes at high dose; histiocytosis in small intestine & mesenteric lymph nodes at mid & high dose. Rat 90-Day Oral Study. 0.8, 12 or 400 mg/kg/day via diet; NOEL = 12 mg/kg/day (based on body-weight gain); 40 mg/kg/day (based on histiocytosis). Food consumption in all treated groups similar to control. Small decrease in body-weight gain in mid-dose males & high-dose males & females; histiocytosis in small intestine & mesenteric lymph nodes at high dose. Dog 90-Day Oral study. 13, 40 or 120 mg/kg/day via diet; NOEL = 13 mg/kg/day. Palatability issues at mid- & high dose. GI clinical signs at mid & high dose (vomiting); histiocytosis in small intestine & regional lymph nodes at mid & high dose. Rabbit 28-Day Percutaneous study. 0.1% or 0.5% aqueous dispersion (2 or 10 mg/kg/day), 5 days/week. Slight (to moderate) skin irritation at both concentrations. No evidence of systemic toxicity.	No data	9,12,13

Table 13. Analog Group 2: PEG-4 Cocamine as a Structure of Interest (SOI)

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-dose Toxicity	Developmental & Reproductive Toxicity (DART)	Ref.
PEG-2 C13-C15 alkyl amine	70955-14-5	13-15	2	No data	Rat 90-Day Oral study. 15, 30 or 150 mg/kg/day via gavage; NOAEL=15 mg/kg/day. Macro & microscopic changes in non-glandular stomach. Dog 90-Day Oral study. 15, 30 or 100 mg/kg/day via capsule; NOAEL 30 mg/kg/day. GI clinical signs: Increased ALT in females only; Increased pigment accumulation in Kupffer cells & bile canaliculi in females only.	No data	10
PEG-8 stearamine	26635-92-7	16-18	8	Ames test: (-)	No data	No data	9,11

Table 14. Analog Group 3: PEG-10 Cocamine as a Structure of Interest (SOI)

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-dose Toxicity	Developmental & Reproductive Toxicity (DART)	Ref.
SOI							
PEG-10 cocamine	61791-14-8	8-16	10	No data	No data	No data	-
Analogs							
PEG-8 stearamine	26635-92-7	16-18	8	Ames test: (-)	No data	No data	[9,11]
PEG-15 tallow amine	61791-26-2	16-18	15	Ames test :(-) *In vivo* mouse micronucleus test: (-)	Rat 90-Day Oral study. 33, 99 & 292 mg/kg/day via diet; NOEL=33 mg/kg/day. GI irritation (hypertrophy & vacuolation of histiocytes in the *lamina propria* of the small intestine); histiocytosis in small intestine & mesenteric lymph nodes at mid & high dose.	Rat Developmental Toxicity Test. 15, 100 or 300 mg/kg/day via gavage on GD 6-15; NOAEL = 300 mg/kg/day (Highest dose tested); Maternal NOAEL = 100 mg/kg/day. Rat 2-generation DART screen. 100, 300 or 1000 ppm in diet. Reproductive / developmental NOAEL = 15 mg/kg/day; LOAEL = 53 mg/kg/day. Litter loss, decreased litter size, & postnatal survival.	[10]
POE-5/POP-12 tallow amine	68213-26-3	16-18	17	No data	Rat 4-Week Oral Study: 15, 75 or 200 mg/kg/day via gavage. NOAEL=75 mg/kg/day; decreased body-weight gain & food consumption at high dose.	No data	[10]
PEG-4 cocamine	61791-14-8	8-16	4	No data	No data	No data	-

Table 15. Analog Group 4: PEG-15 Cocamine as a Structure of Interest (SOI)

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-dose Toxicity	Developmental & Reproductive Toxicity (DART)	Ref.
SOI							
PEG-15 cocamine	61491-14-8	8-16	15	No data	No data	No data	-
Analogs							
PEG-10 cocamine	61791-14-8	8-16	10	No data	No data	No data	-
POE-5/POP-12 tallow amine	68213-26-3	16-18	17	No data	Rat 4-Week Oral Study. 15, 75 or 200 mg/kg/day via gavage. NOAEL = 75 mg/kg/day. Decreased body-weight gain & food consumption.	No data	10
PEG-8 stearamine	26635-92-7	16-18	8	Ames test: (-)	No data	No data	9,11
PEG-15 tallow amine	61791-26-2	16-18	15	Ames test: (-) *In vivo* mouse micronucleus test: (-)	Rat 90-Day Oral Study. 33, 99 & 292 mg/kg/day via diet. NOEL = 33 mg/kg/day. GI irritation, histiocytosis in small intestine & mesenteric lymph nodes at mid & high dose.	Rat Developmental Toxicity Study: 15, 100 or 300 mg/kg/day via gavage on gestation days 6-15. NOAEL 300 = mg/kg/day. Rat 2-Generation DART Study. NOAEL = 15 mg/kg/day; NOAEL = 15 mg/kg/day; LOAEL = 53 mg/kg/day. Litter loss, decreased litter size & postnatal survival.	10
PEG-20 tallow amine	61791-26-2	16-18	20	Ames test: (-) *In vitro* mouse lymphoma test: (-) *In vitro* UDS test: (-) *In vitro* chromosome aberration test: (-) without S-9; (+) with S-9 *In vivo* mouse chromosome aberration test: (-)	Rabbit 28-Day Percutaneous Study: 10% aqueous dispersion, reduced to 2% aqueous dispersion after 2 treatments (200 mg/kg/day reduced to 40 mg/kg/day), *5* days/week for 4 weeks. Severe skin irritation at 10% leading to reduction in concentration to 2%. No evidence of systemic toxicity. Rabbit 28-Day Percutaneous Study: 2% aqueous dispersion (40 mg/kg/day), *5* days/week for 4 weeks. Severe skin irritation. No evidence of systemic toxicity.	No data	9

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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: April 21, 2015

SUBJECT: Summaries of Sensitization Studies PEG-2 Tallow Amine

Hill Top. 1978. Summary of a delayed contact hypersensitivity study of PEG-2 Tallow Amine in guinea pigs.

Study Type: Delayed Contact Hypersensitivity Study in Guinea Pigs
Date: 05/03/78
Laboratory: Hill Top
Results: 20 guinea pigs were in the test group and 10 in the control group. Induction (2.6%) and challenge (0.6%) doses employed different solvents. 2.6% in ethanol showed irritation scores of 0, 1, and 2, but no details provided on irritation scores during induction using 2.6% in ethanol. 0.6% in acetone showed irritation scores of 0, and the control and test animals during challenge showed mainly scores of 0. There were no indications of sensitization.

Conclusions: PEG-2 Tallow Amine did not induce sensitization in guinea pigs.

MB Laboratories. 2002. Local lymph node assay of PEG-2 Tallow Amine in mice.

Study Type: LLNA Sensitization in Mice
Date: 2002
Laboratory: MB Laboratories

Results: Groups of five CBA mice were treated by topical application of PEG-2 Tallow Amine (0.1, 0.3, 1.0% v/v) once daily to the dorsum of each ear for three consecutive days. Additional groups were treated with the known sensitizers

DNCB (0.25% w/v) or HCA (50% v/v), or the false-positive irritant SLS (25% w/v). Five days following the initial dose, the mice were injected (i.p.) with 5-bromo-2'-deoxy-uridine (BrdU) to label proliferating cells. Auricular lymph nodes were isolated and the number of BrdU+ cells was determined for individual animals by flow cytometry. Immunophenotype analysis of the nodal cells was conducted using the marker combinations B220/CD3 and IA/CD69 to determine the B:T cell ratio and the activation state of the nodal lymphocytes respectively. Ear thickness was also evaluated for all animals. PEG-2 Tallow Amine caused a significant increase in ear thickness and a dose-dependent increase in lymph node cell proliferation with a maximum Stimulation Index (SI) of 125.9 (EC3 < 0.1%), while the known sensitizers DNCB and HCA gave a SI of 104.6 and 30.1 respectively. Higher dose levels of PEG-2 Tallow Amine and both positive control substances also caused a significant increase in the B:T cell ratio and in the % of IA+/CD69+ cells. Treatment with SLS resulted in significant ear swelling and an SI of 3.2 but no increase in cellular markers. Despite the significant irritant response induced by PEG-2 Tallow Amine, the magnitude of the proliferative response and the activation state of cells localized in the nodes of treated mice identify PEG-2 Tallow Amine as a potential dermal sensitizer.

Conclusions: PEG-2 Tallow Amine may be a skin sensitizer to hypersensitive individuals.

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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: March 12, 2015

SUBJECT: Comments on the Draft Report Prepared for the March 16-17, 2015 CIR Expert Panel Meeting: Safety Assessment of PEGs Cocamine and Related Ingredients as Used in Cosmetics

Key Issue

As there are genotoxicity assays and a 28-day dermal toxicity study on PEG-2 Tallow Amine, the conclusion for ingredients with a predominantly 18 carbons in length (all ingredients but Lauramine and Cocamine) should be changed to safe for use in hair dye products and insufficient data for other uses.

Additional Comments

Reproductive and Developmental Toxicity, PEG-2 Cocamine - Did the rats at 2000 ppm really loose weight (reference 9), or did they observe a reduction in body weight gain?

Reproductive and Developmental Toxicity PEG-15 Tallow Amine - Please correct "and until sacrificed"

Genotoxicity - Please indicate the types of studies in which PEG-15 Cocamine was negative for genotoxicity. The information on PEG-8 carcinogenicity should be in a carcinogenicity section.

Genotoxicity, PEG-20 Tallow Amine - The subheading is PEG-20 Tallow Amine, but this section also mentions studies on PEG-2 Tallow Amine (or PEG-2 Tallow Amine should be PEG-20 Tallow Amine).

Application of the Framework to Evaluate PEGs Cocamine Ingredients, Ethoxylated C13-15 alkylamines - It does not make sense to have "Ethoxylated" in the heading then to say that the analog is not "ethoxylated". Is this a hydroxyethyl rather than a polyethoxylated compound?

Summary - The Summary should indicate that there are reproductive and developmental toxicity data available on PEG-2 Cocamine.

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Wave 2, Acute Exposure, Oral, PEG-20 Tallow Amine - In the second paragraph it says "PEG-20 tallow amine (aka ethanol, 2,2-'iminobis-, N-tallow alkyl derivatives)" - the second name is not correct for PEG-20 Tallow Amine. As the correct second name "(aka $(POE)_{20}$ tallowamine)" is given in the first paragraph, it is not necessary to repeat the second name in the second paragraph of this section.

Please use the same units throughout the second paragraph. Currently, the doses are given as g/kg, then mg/kg and then it switches back to g/kg.

Wave 2, Table 2, Lauramine & Stearamine - Please correct: "No use concentrations of frequencies reported".

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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: April 21, 2015

SUBJECT: Comments on the Tentative Amended Report: Safety Assessment of PEGs Cocamine and Related Ingredients as Used in Cosmetics

Key Issues

In multiple places, including the Chemistry section, Summary and Table 1, the report describes the smaller PEG compounds and states "or one monoethoxyl group and one polyethoxyl group if x=0 and y=2". This is not correct. If x=0 there would be no ethoxyl groups. Instead of an ethoxyl group there would be one hydrogen bound to the nitrogen. Based on the method of manufacture in which the PEG-2 compounds are formed before the PEG chains are elongated, the case in which x=0 and y=2 is unlikely. This is supported by information from suppliers that indicates only low levels of primary and secondary amines in these ingredients and the level of primary and secondary amines does not appear to decrease as the average level of ethoxylation increases.

Additional Comments

Introduction - In the first paragraph, it is not necessary to include both soy acid and soy oil in the list components of these ingredients.

Repeated Dose Exposure, POE-5/POP-12 tallow amine - It is not clear why gavage dosing with POE-5/POP-12 tallow amine reduced the palatability of the diets. Was this really a gavage study?

Reproductive and Developmental Effects, PEG-2 Cocamine - Please revise "were exposed to diets" to " were fed diets"

Genotoxicity - Please summarize the genotoxicity studies in a table.

PEG-20 tallow amine - Please revise "treated related"

Carcinogenicity - Please provide a few more details about the carcinogenicity studies of PEG-8, e.g., species, dose.

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Irritation and Sensitization - In the summary from the previous report, please include some indication of the concentrations that were tested.

Throughout the description of the SAR, DEREK® needs to be replaced with Derek for Windows™