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

Status:	Draft Final Amended Report for Panel Review
Release Date:	February 20, 2015
Panel Meeting Date:	March 16-17, 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 safety assessment 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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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer, PhD, DABT
Senior Toxicologist
Date: February 20, 2015
Subject: Tentative Amended Safety Assessment of PEGs Cocamine and Related Ingredients

Enclosed is the tentative amended safety assessment report for PEGs cocamine and related ingredients (*pgcoca032015_TAR* in the pdf document).

At the December 2014 meeting, the Panel expressed support for developing an SAR-based framework as a systematic approach to identifying and evaluating analogs for read across. However, the Panel emphasized the importance of developing quantitative measures for the key decision-making steps, characterizing boundary conditions and assumptions of models, and using adequate test data to validate computational predictions. In addition, the Expert Panel noted data gaps for the PEGs cocamine and related ingredients.

However, the Panel found that the available data and the SAR-based read-across analysis presented in the strategy memorandum at the December 2014 meeting can support the safety of 32 of the 47 PEGs cocamine ingredients. The Panel noted that products containing these ingredients should be formulated to be non-irritating, and to minimize the potential formation of hydroperoxides through autoxidation. They noted also that Industry should continue to use the necessary procedures to limit 1,4-dioxane, ethylene oxide, aflatoxin, residual pesticides and heavy metals as impurities in PEGs cocamine and related ingredients, and to preclude the potential transfer of infections agents from the ingredients derived from animal tissues.

In contrast, the Panel found that the information was insufficient to determine the safety of the 15 PEGs cocamine and related ingredients with $x+y \leq 5$. The additional data needed for these ingredients include:

(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.

The tentative amended safety assessment report is accompanied by the following attachments:

- Transcript of the December 2014 CIR Expert Panel meeting (*pgcoca122014tmin*)

The minutes 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, Industry submitted several reports and additional information since the December 2014 meeting, including:

- Requested studies to support the safety of PEG cocamine ingredients (*pgcoca032015data_1*)
  - Salmonella/mammalian mutagenicity assay of PEG-8 stearamine (*pgcoca032015data_1*)
  - 13-week oral (dietary) toxicity study of PEG-2 tallow amine (*pgcoca032015data_2*)
  - 4-week percutaneous toxicity study of PEG-2 tallow amine (*pgcoca032015data_3*)
- Analytical information on PEG-2 tallow amine from the oral study (*pgcoca032015data_4*)
- Tertiary amine content of PEG fatty-acid amine ingredients (*pgcoca032015data_5*)
- Animal sensitization test summaries of PEG-2 hydrogenated tallow amine (*pgcoca032015data_6*)
- Composition PEG-2 and PEG-5 cocamine (*pgcoca032015data_7*)
- Patch test of hair dye formulation containing PEG-5 soyamine (*pgcoca032015data_8*)

Industry submitted comments on the draft tentative report posted for public comment, including:

- Comments on the tentative safety assessment, 21 January 2015 (*pgcoca032015PCPC_1*)
- Comments on the tentative safety assessment, 29 January 2015 (*pgcoca032015PCPC_2*)
- CIR Science and Support Committee comments, 29 January 2015 (*pgcoca032015PCPC_3*)

The tentative amended report reflects the information submitted, including:

- Tallow amine phosphate ester is described as a secondary amine in the documentation obtained from US EPA; this ester was thus removed from among the analogs identified for the ingredients

- Data for several of the fatty acids from which the ingredients are derived are predominantly tertiary amines (eg, > 95% to 100% for PEG-2 through PEG-5 cocamine)

In their submission, the CIR SSC recommended the following (*pgcoca032015PCPC_3*):

- Develop a conclusion that applies explicitly to ingredients that conform to the composition information available from the suppliers, which indicates the predominance of tertiary amines

- Read across from the genotoxicity and 28-day toxicity test data for PEG-2 tallow amine to assess the safety of PEGs oleamine, PEG-2 rapeseedamine, and other ingredients in which fatty-acid moieties 16 to 18 carbons long predominate (ie, PEGs soyamine, PEGs stearamine, PEGs tallow amine and PEGs hydrogenated tallow amine)

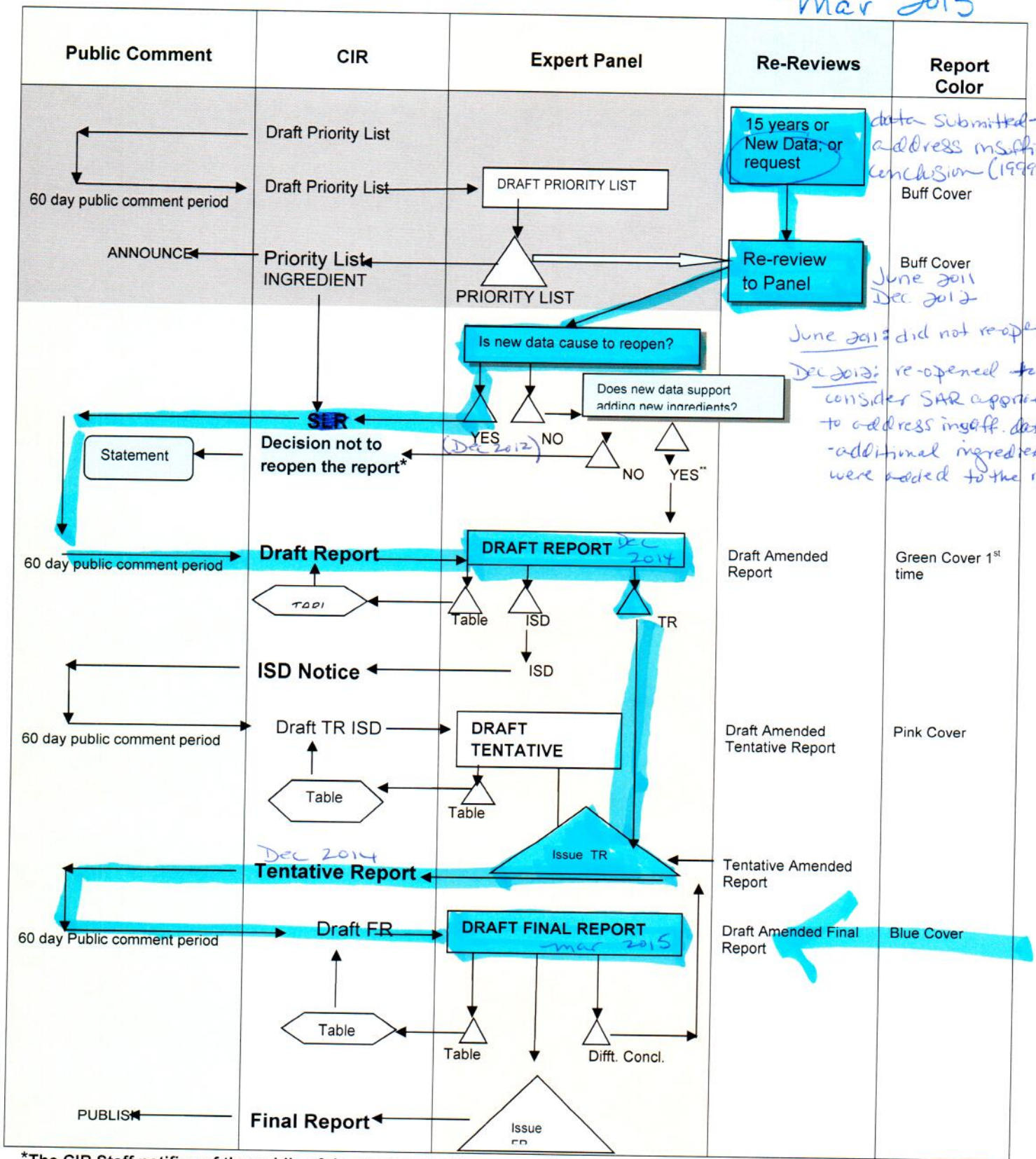
- Develop a safe-as-used in hair dye products conclusion for PEG-2 oleamine, PEG-2 rapeseedamine, and other ingredients with 16- to 18-carbon fatty-amine chains predominating, because sensitization data are not needed for rinse-off products requiring patch testing before use

- Delete the safety information for polyoxyethyleneamine tallow amine presented in the Non-Cosmetic Use section of the tentative 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 or revise the Panel's tentative conclusion as stated at the December 2014 meeting.

Also, please consider that some of the data presented in the safety assessment report are from studies on the predominant surfactant in a commercial herbicide preparation. The surfactant is referred to as "polyoxyethyleneamine tallow amine" (aka polyoxyethyleneamine or POEA), and is described as a mixture of polyethoxylated long-chain alkylamines synthesized from animal-derived fatty acids. We do not have detailed characterization data for the surfactant, and we do not have copies of the unpublished reports from which the toxicology data were derived in the published papers that we reviewed. The Panel should decide whether to keep the summary information for this substance in the safety assessment report, or to delete it as irrelevant or superfluous for assessing the safety of the PEGs cocamine and related ingredients.

SAFETY ASSESSMENT FLOW CHART



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

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

Expert Panel Decision

Document for Panel Review

Option for Re-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.

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												
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

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?

MS. 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 for Panel Review
Release Date: February 20, 2015
Panel Meeting Date: March 16-17, 2015

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ABSTRACT

The CIR Expert Panel assessed the safety of 47 PEGs cocamine and related ingredients. These ingredients comprise mixtures of mostly tertiary amines that have alkyl groups derived from plant or animal fatty and average numbers of polyethylene glycol groups equal to the number in the chemical name. Most of these ingredients are reported to function as surfactants or antistatic agents. The Panel reviewed the available test data and a structure activity relationship (SAR)-based read-across assessment to evaluate the safety of these ingredients. The Panel concluded that 32 of these ingredients are safe 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. The data were insufficient to determine the safety of the 15 other ingredients included in this safety assessment, all of which have PEG-2, -3, -4, or -5 in the ingredient names.

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 derivatives of the fatty acids of coconut oil, lauramine, oleic acid, palmitamine, rapeseedamine, soy acid, soy oil, 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. PEG-5soyamine is reported to be used in hair bleaches, hair-coloring preparations, or hair lighteners with color, and PEG-2 rapeseedamine is used in hair dyes and colors requiring caution statements and patch tests.

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 Expert 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 greater detail in the Appendix of this safety assessment. 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 structural 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 Expert 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 read-across analysis presented in these two CIR SSC submissions,[4,5] and illustrated in Dr. Blackburn's presentation to the Panel,[6] indicates that these ingredients will not exhibit genotoxicity or systemic toxicity when used as intended in cosmetics. In addition, the CIR SSC's submissions included data and computational analyses indicating that the PEGs cocamine, like the PEGs, are not dermal sensitizers.[4,5,7]

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[8,9] and three unpublished reports cited in one of the HPV reports.[10-12] 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, and possibly some toxicity information published on a polyoxyethyleamine tallow amine (the predominant surfactant in a commercial herbicide formulation).

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.

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]

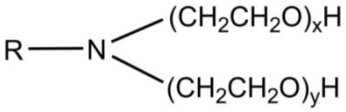


Figure 1. General chemical structure of PEGs cocamine and related ingredients

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 polyethylene glycol moieties and various lengths and degrees of unsaturation of the alkyl fatty acid moieties (Table 1).[13]

The structure of PEG-2 cocamine and the other ingredients in this group with PEG-2 in the INCI name will have two monoethoxyl groups, rather than two polyethoxyl groups, if x and y both equal 1, or one monoethoxyl group and one polyethoxyl group, if x=0 and y=2. The CIR Expert Panel noted the possibility of similar structural variations for ingredients with PEG-3, -4, and -5 in the INCI name (Table 1).[13]

In coconut oil, saturated fatty acids with chain length of C12 (44% to 53%) predominate, and there were smaller fractions of unsaturated C16 (0% to 1%) and C18 (6% to 12%) chains (Table 2).[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 3).[4]

Unsaturated fatty acids with chain lengths of C18 predominate in rapeseed oil (>32% to >96%; Table 4) and in soybean oil (>40% to >60%) (Table 5).[14]

Chemical and Physical Properties

Supplier specifications and analytical data for some of the PEGs cocamine and related ingredients are presented in Table 6. 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.[15]

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.

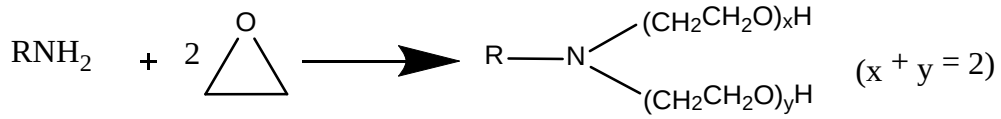


Figure 2. Ethoxylation of fatty amines, Step 1

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.

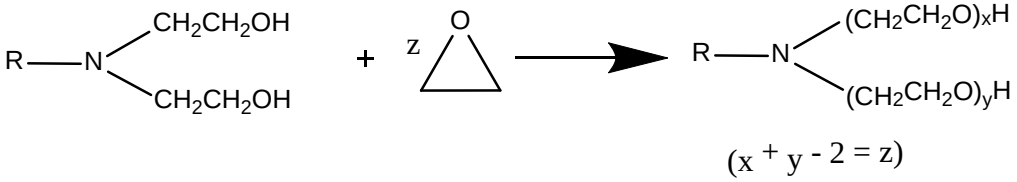


Figure 3. Ethoxylation of fatty amines, Step 2

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 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.

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 6), 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).[16] 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;[2,15,17] 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 6).[18]

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated based on the expected use in cosmetics. The Panel utilizes data received from the Food and Drug Administration (FDA) and the cosmetics industry in determining the expected cosmetic use. The data received from the FDA are those it collects from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP), and those from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations by category conducted by the Council.

According to the 2014 VCRP survey data, PEG-2 rapeseedamine is reported to be used in 255 hair coloring (rinse-off) formulations, and PEG-2 oleamine is reported to be used in 239 hair coloring formulations (Table 7). All of the in-use ingredients were reported to be used in rinse-off products, except PEG-2 oleamine, which was reported to be used in one leave-on product.(other hair coloring preparations). 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 0.16% PEG-2 oleamine in other hair coloring preparations.

The frequency of use totaled 107 for PEG-2 cocamine in 2014, compared to 15 in 1996, and 4 for PEG-15 cocamine in 2014, 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[19,20]

Tables 7 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 that are reported to be used.

Table 9 lists the 37 PEGs-cocamine and related ingredients not indicated to be in use, based on the 2014 VCRP data and the results of the Council 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.[21,22] 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.[23,24]

Non-Cosmetic

The predominant surfactant in a commercial herbicide formulation is a polyoxyethyleneamine tallow amine (aka polyoxyethyleneamine or POEA),[25,26] which is a mixture of polyethoxylated long-chain alkylamines synthesized from animal-derived fatty acids.[26] The molecular size of POEA is not specified in the literature. However, its size probably fits into the range of sizes of the ingredients used in cosmetic products.

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).[26] POEA is listed by US EPA as a pesticide inert ingredient.[27].

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.*

Polyoxyethyleneamine tallow amine (aka POEA) of a herbicide formulation

The predominant surfactant in a commercial herbicide formulation is a polyoxyethyleneamine tallow amine (POEA),[25,26] which is a mixture of polyethoxylated long-chain alkylamines synthesized from animal-derived fatty acids.[26] A published article summarized several unpublished studies on the POEA, as well as other components of this formulation.[26] The results reported specifically for POEA included acute oral (rats) and dermal (rabbits) LD_{50} of 1200 mg/kg and 1260 mg/kg, respectively.

Groups of at least 5 Sprague-Dawley rats weighing 340-360g were exposed to 1, 3 or 5 ml of a 7% solution of POEA (in saline) by a single injection of the solution directly into the stomach of each animal.[28] The saline vehicle was injected into the stomachs of the control rats. About 23 hours later, the animals were killed by fluothane overdose, and the gross necropsy examination was performed, including scoring (0 = no damage and 5 = complete hemorrhage of the whole lung) of the lungs. There was no substantial difference in the lung weights or scores for any of the saline or POEA exposed rats. Treatment with 3 or 5 ml of the POEA solution was associated with some blood stained weeping from the nose and bronchi, wheezing, piloerection, and diarrhea.

Groups of at least 5 Sprague-Dawley rats weighing 340-360g were exposed to 0.1, 0.2, or 0.4 ml of a 7% solution of POEA (in saline) by a single injection of the solution directly into the trachea of each animal.[28] The saline vehicle was injected into the trachea of the control rats. About 23 hours later, the surviving animals were killed by fluothane overdose, and the lungs of these rats, as well as those that died during the post-dosing observation period, were dissected free from other structures, blotted and evaluated. Each lung was scored on a scale of 0 to 5 (0 = no damage and 5 = complete hemorrhage of the whole lung). POEA produced 20%, 70%, and 100% death at 0.1, 0.2, and 0.4 ml, respectively. POEA increased lung weights from 1.4 g at 0.1 ml to 2.3 at 0.2 and 0.4 ml. The lungs were damaged and the atria were engorged with blood, although other organs appeared normal.

Repeated Dose Toxicity

Oral

PEG-2 tallow amine (aka ethanol, 2,2'-iminobis-,N-tallow alkyl derivatives)

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.[4,5,8] 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 NOEL was 500 ppm (about 50 mg/kg/day) and the 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.[4,5,8,12,29] The test substance was added to the diets as 1% solutions in corn oil. The rats were about 6-½ weeks of age. 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 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.[4,5,8] 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 LOAEL was 50 mg/kg/day. No other findings of this study were presented.

Ethoxylated C13-C15 alkylamines

Ethoxylated C13-C15 alkylamines was tested in rats in a 90-day oral repeated dose toxicity study.[9] Ethoxylated C13-C15 alkylamines is not identified as a cosmetic ingredient in the *International Cosmetic Ingredient Dictionary and Handbook*. However, like PEG-2 cocamine and related ingredients, ethoxylated C13-C15 alkylamines (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 ethoxylated C13-C15 alkylamines by gavage for 90 days. The control groups were given deionized water.[9] 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 (aka tallow, POE 15) was administered in the diet *ad libitum* to three groups of 10 male and 10 female Sprague-Dawley rats.[9] 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 (aka tallow, POE n=5/12)

POE-5/POP-12 tallow amine was tested in rats in a 28-day oral repeated dose toxicity study.[9] This substance is not identified as a cosmetic ingredient in the *International Cosmetic Ingredient Dictionary and Handbook*. 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 reduced palatability of the diets. 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.

Polyoxyethyleneamine tallow amine (aka POEA) of a herbicide formulation

Groups of Sprague–Dawley rats (n not specified) received 0, 800, 2000, or 5000 ppm POEA in the diet for 1 month.[26] No additional information about the experimental protocol was provided. Body weight gains were reduced in males at 2000 ppm and in both sexes at 5000 ppm. Prominent, enlarged lymphoid aggregates in the colons of the females exposed to 5000 ppm POEA were associated with direct irritation or inflammatory reponse attributed to POEA.

In a subsequent 3-month study, groups of with rats, POEA was administered in the diet at concentrations of 0, 500, 1500, and 4500 ppm.[26] Effects noted among the animals exposed to 4500 ppm POEA included intestinal irritation, decreased food consumption and body weight gain, and some alterations in serum hematology and clinical

chemistry parameters. Intestinal irritation was observed also in some animals of the 1500 ppm group. The NOAEL was reported to be 500 ppm POEA in the diet (approximately 36 mg/kg/day for males and females combined).

Beagle dogs (n not specified) received 0, 30, 60, or 90 mg/kg/day POEA in gelatin capsules for 10 weeks, after 4 weeks of receiving the test substance in gradually increasing doses(because of emesis and diarrhea observed during the preliminary stage of this study)

.[26] Body weights were reduced in dogs of the 90 mg/kg/day group. Body weights were reduced also in the females of the 60, or 90 mg/kg/day females, although there was no evident dose-response relationship. Slight reductions in serum calcium and protein in the dogs of the 60, or 90 mg/kg/day were equivocal. The most noteworthy observation of this study was the inability of dogs to tolerate daily ingestion of the surfactant because of gastrointestinal irritation.

Percutaneous

PEG-2 tallow amine (aka ethanol, 2,2-iminobis-, N-tallow alkyl derivatives)

Two groups of 5 young adult New Zealand White rabbits of each sex (2.5 to 3.3 kg body weight) were exposed dermally to 0.1 or 0.5% PEG-2 tallow amine dispersed in water.[4,5,8,11,29] 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 (aka polyethoxylated tallow amine) 5 days/week.[5,8] 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) weighing 2 to 3 kg were treated with a 2 ml/kg of a 2% w/v aqueous suspension of PEG-20 tallow amine (aka $(POE)_{20}$ tallowamine) 5 days/week.[5,8] 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.

PEG-2 cocamine

In a combined repeated dose toxicity study and DART screening test, groups of 24 Crl:CD(SD) rats (12 males and 12 females) were exposed to diets containing 0, 30, 100, 300, or 2000 ppm PEG-2 cocamine (aka coco, POE n=2) for 14 consecutive days prior to mating (males and females) and throughout gestation and day 4 of lactation (females).[9] 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 (aka tallow, POE n+15)

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.[9] 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.[9] The parental animals of the first generation (F_0) were exposed to the test substance for at least 70 days before mating, and until 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.

Polyoxyethyleneamine tallow amine (aka POEA) of a herbicide formulation

Groups of pregnant Sprague–Dawley rats (n not specified) received 0, 15, 100, or 300 mg/kg/day POEA by gavage on gestation days 6 through 15.[26] No additional description of the experimental protocol was provided. Substantial maternal toxicity was observed at 300 mg/kg/day, and minimal effects (decreased food consumption and mild clinical signs) at 100 mg/kg/day. There were no effects on the fetuses at any dose. The NOAELs reported for maternal and developmental toxicity were 15 mg/kg/day and 300 mg/kg/day, respectively.

GENOTOXICITY

In mutagenicity studies, PEG-15 cocamine was negative. 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. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously.

***PEG-2 tallow amine (aka ethanol, 2,2'-iminobis-,N-tallow alkyl derivatives*)**

PEG-2 tallow amine was negative for mutagenicity in a *Salmonella*/mammalian microsome mutagenicity assay (Ames test).[4,5,8] PEG-2 tallow amine was tested using TA98, TA100, TA1535, TA1537, and TA1538 bacterial strains. Solvent (ethanol) controls and each test-substance concentration was assayed in triplicate. Positive control substances (2-nitrofluorene, 1,2-propane sultone, and 9- aminoacridine) were tested without replication. The test compound was assayed at up to 0.08 µl/plate. PEG-20 tallow amine did not increase the number of revertants per plate with or without metabolic activation (ie, Aroclor-induced rat liver microsomes).

PEG-2 tallow amine was negative in a mouse micronucleus (MN) assay performed in accordance with OECD methods and guidelines.[4,5,8] Groups of 30 mice (15 of each sex/group) were given a single 10,860 mg/kg dose of PEG-2 tallow amine by gavage. Two additional groups of 30 mice (15 of each sex/group) served as controls, including one group given distilled water by gavage (negative control), and the other group given mitomycin C by ip injection (positive control). Five males and five females from each group were sacrificed 24, 48 and 72 hours after exposure, and one bone marrow smear was prepared from the femurs of each mouse. Stained smears were

examined for micronucleated cells by light microscopy, and the ratio of polychromatic to normochromatic erythrocytes was calculated based on results from at least 1000 erythrocytes/animal. One male animal died about 30 hours after treatment with PEG-2 tallow amine. Clinical signs observed 72 hours after exposure to the test substance included slight pallor of the extremities, diarrhea, slight-to-moderate piloerection, lethargy, decreased respiratory rate and ptosis, walking on toes, and greasy fur. None of the control mice (negative or positive) exhibited clinical reactions. A statistically-significant increase in the number of micronucleated polychromatic erythrocytes was found 24 hours after exposure to PEG-2 tallow amine. Increases in this parameter were not statistically significant 48 and 72 hours after exposure. These findings were not considered to be treatment related, because they were well within the ranges of historical controls. 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. The positive control compound, mitomycin C, produced statistically-significantly increased frequencies of micronucleated polychromatic and normochromatic erythrocytes, and decreased ratios of polychromatic to normochromatic erythrocytes. The single mortality and the increased numbers of micronucleated polychromatic erythrocytes after treatment with PEG-2 tallow amine were not considered to be treatment related. However, the PEG-2 tallow amine was toxic to bone marrow cells at the dose tested in this study.

PEG-2 tallow amine was negative in an in vivo cytogenicity study using Sprague-Dawley rats.[4,5,8] Groups of 10 rats (5 of each sex/group) were given 39, 130, or 390 mg/kg/day of the test substance by gavage for 5 consecutive days. Two additional groups of 10 rats (5 of each sex/group) served as controls, including one group given distilled water by gavage (negative control), and the other group given methylmethane sulfonate (MMS) by gavage (positive control). All of the animals received 1 mg.kg colchicine by ip injection 20 hours after the last treatment, to inhibit mitosis, and were sacrificed 2 to 4 hours later. Bone marrow smears were prepared from both femurs of each animal. About 50 metaphase spreads per mouse were examined for cytogenetic abnormalities, including deletions, exchanges, rings, gaps and breaks, and mitotic index was calculated for mouse. All animals exposed to 390 mg/kg/day PEG-2 tallow amine and 2 females exposed to the lower doses of PEG-2 tallow amine developed diarrhea. Some of the treated animals exhibited red-brownish exudates around the eyes and mouth, but this was not considered to be treated related. The positive control yielded the expected results. PEG-2 tallow amine did not induce chromosome aberrations in this study.

PEG-8 stearamine (aka alkylamineethoylate)

PEG-8 stearamine is not identified as a cosmetic ingredient in the *International Cosmetic Ingredient Dictionary and Handbook*, unlike PEG-2, -5, -10, -15, and -50 stearamine (Table 1). However, PEG-8 stearamine is a likely analog for these ingredients in a read-across assessment. PEG-8 stearamine was negative for mutagenicity in an Ames test. PEG-8 stearamine in water was tested at 0.0008 to 0.08 µl/plate using TA98, TA100, TA1535, TA1537, and TA1538 bacterial strains.[8,10,29] PEG-8 stearamine was tested using TA98, TA100, TA1535, and TA1537 bacterial strains. Solvent (water) controls and each test-substance concentration were assayed in triplicate. Positive control substances (2-nitrofluorene, 1,2-propane sultone, and 9- aminoacridine) were tested without replication. The test compound was assayed at up to 0.08 µl/plate. PEG-8 stearamine did not increase the number of revertants per plate with or without metabolic activation (ie, Aroclor-induced rat liver microsomes).

PEG-15 tallow amine

PEG-15 tallow amine was negative for mutagenicity in a *Salmonella*/mammalian microsome mutagenicity assay (Ames test).[9] PEG-15 tallow amine was tested using TA98, TA100, TA1535, TA1537, and TA1538 bacterial strains. The solvent and positive control substances were not specified. The test compound was assayed at up to 300 µg/plate without metabolic activation and up to 1000 µg/plate with metabolic activation (S9 mix). PEG-15 tallow amine tested up to cytotoxic concentrations did not increase the number of revertants per plate, with or without metabolic activation. The positive controls yielded the results expected.

PEG-15 tallow amine was negative in a mammalian micronucleus (MN) assay in which the dose of the test substance was 100 mg/kg.[9] There was no increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any harvest time up to a maximum tolerated doss (MTD). No further details were provided.

PEG-20 tallow amine (aka $(POE)_{20}$ tallow amine)

PEG-20 tallow amine was negative for mutagenicity in a *Salmonella*/mammalian microsome mutagenicity assay (Ames test).[4,5,8] PEG-20 tallow amine was tested using TA98, TA100, TA1535, TA1537, and TA1538 bacterial strains. Solvent (water) controls and each test-substance concentration was assayed in triplicate. Positive control substances (2-nitrofluorene, 1,2-propane sultone, and 9- aminoacridine) were tested without replication. The test compound was assayed at up to 0.08 µl/plate. PEG-20 tallow amine did not increase the number of revertants per plate with or without metabolic activation (ie, Aroclor-induced rat liver microsomes).

PEG-20 tallow amine (purity 99.5%) was negative in a mouse lymphoma mutation assay, using $TK^{+/-}$ L5178Y cells in culture.[4,5,8] PEG-2 tallow amine was diluted in ethanol to prepare 0.0013 to 0.1 µl/ml solutions of the test substance for the assay without metabolic activation, and approximately 10 µl/ml solutions for the assay with metabolic activation (ie, Aroclor-induced rat liver microsomes). The test substance was added to samples of the cell culture to yield a final suspension of 3×10^5 cells/ml. PEG-2 tallow amine was tested at 0.33, 1.0, 3.3, 10, 33 and 100 µg/plate. Ethanol served as the solvent control, and ethyl methane sulfonate (EMS) and 7,12-dimethylbenz[a]-anthracene (DMBA) as positive controls. The cells were washed after a 4-hour exposure period, resuspended and incubated for 2 days, maintaining a continuous active growth state of the cells throughout the 2-day expression period. Cultures exhibiting 10% to 90% relative growth inhibition were then transferred to a cloning medium for duplicate cloning, one with trifluorothymidine (TFT)/ml as a selective agent and the other for counting viable cells. Following incubation for 10 to 12 days in the cloning medium, the plates were scored and the total numbers of colonies/plate and the mutation frequencies were calculated. None of the cloned cultures exposed to PEG-2 tallow amine, with or without metabolic activation, exhibited greater mutation frequencies compared with those of the solvent controls.

PEG-2 tallow amine was negative in a cell chromosome aberrations test without metabolic activation, but positive with metabolic activation.[4,5,8] The test was performed using Chinese hamster ovary (CHO). PEG-2 tallow amine was diluted in ethanol to prepare solutions added to the cells (final density 5×10^6 cells/ml) to yield maximum test-substance concentrations of 0.03 µl/ml for the assay without metabolic activation, and 0.3 µl/ml for the assay with metabolic activation (ie, Aroclor-induced rat liver microsomes). Ethanol served as the solvent control, and triethylenemelamine (TEM) and cyclophosphamide (CP) as positive controls. The cells were washed after a 4-hour exposure period, resuspended and incubated again for 16 hours (expression period). The cells were then treated with colcemid (1 µg /ml) and incubated for 2 more hours. Metaphase cultures were harvested, cytotoxicity was estimated, and slides were prepared from fixed cells and scored (50 metaphase spreads scored for each concentration) for number of metaphase chromosomes, gaps, chromatid breaks and fragments, chromosome breaks, exchange figures, dicentria, rings, polyploids, pulverization and severely damaged cells (ie, >10 aberrations). Cytotoxicity was observed at >0.01 µl/ml PEG-2 tallow amine with metabolic activation and >0.03 µl/ml without activation. PEG-2 tallow amine increased the numbers of chromosome aberrations with metabolic activation in a concentration-dependent manner, compared with the solvent controls. Without metabolic activation, the numbers of aberrations appeared to be elevated, but no concentration-response relationship was detected.

PEG-2 tallow amine was negative in an unscheduled DNA synthesis (UDS) test using a freshly prepared primary rat hepatocyte culture.[4,5,8] The primary culture was prepared from the liver of a male Sprague-Dawley rat, and the cells were allowed to attach to microscope cover slips for up to 2 hours. PEG-2 tallow amine was diluted in ethanol to prepare solutions added to the samples of the cell culture to yield test-substance concentrations ranging from 0.008×10^{-4} to 0.23×10^{-4} µl/ml. Ethanol served as the solvent control, and DMBA dissolved in dimethyl sulfoxide (DMSO) as the positive control (DMSO does not induce UDS at the concentrations used). The cultures were exposed to 10 µCi/ml ^{3}H-thymidine and PEG-2 tallow amine, DMBA (positive control), or ethanol (solvent control) for 18 to 20 hours, and then scored for toxicity and processed for autoradiography. Substantial cytotoxicity was observed at PEG-2 tallow amine concentrations > 0.052×10^{-4} µl/ml. The net nuclear grain counts of the solvent and positive controls were in the acceptable range, and the positive control induced a UDS response, as expected. PEG-2 tallow amine did not induce UDS at any of the concentrations tested in this study.

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.

No dermal irritation or sensitization studies were found or submitted for PEG-2 cocamine. However, several studies were submitted on other ingredients.

Non-Human

Five young adult New Zealand White rabbits of each sex (2.5 to 3.3 kg body weight) were treated with 0.1 or 0.5% PEG-2 tallow amine (aka ethanol, 2,2-iminobis-, N-tallow alkyl derivatives) dispersed in water.[4,5,8,11] 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 was 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 hydrogenated tallow amine did not induce sensitization in guinea pigs in a test for delayed contact hypersensitivity.[30] 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 hydrogenated 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 hydrogenated tallow amine appeared to be sensitizing to mice in a local lymph node assay (LLNA).[30] In this test, 0.1%, 0.3%, or 1.0% PEG-2 hydrogenated allow amine, or 0.25% dinitrochloro-benzene (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 hydrogenated 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 hydrogenated tallow amine (ie, 0.3% and 1.0%) or either of the positive control substances was associated with substantially increased B:T cell 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 hydrogenated tallow amine was very irritating, the magnitude of the cellular responses indicate that dermal application of this substance may be sensitizing.

Human

Two dermal sensitization human repeat insult patch tests (HRIPTs) were submitted for PEG-15 cocamine.[4,31,32] 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).[32]

In the other test, a leave-on hair styling formulation containing 1.0% PEG-15 cocamine was not sensitizing in 212 subjects.[31] During the induction phase of the study, the formulation was applied neat to the skin of normal volunteers, 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.

A hair dye formulation containing 3.4% PEG-5 soyamine caused transient mild-to-moderate signs of irritation in an open application patch test.[33,34] A single 0.5 ml of the undiluted formulation was applied to the inner forearm of each of 12 healthy volunteer 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 the CIR in 2011.[4,35,36] 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

Analog Selection

The framework for identifying and evaluating analogs applied in this safety assessment is described and explained in the Appendix of this report.

Across the PEGs cocamine ingredients, there are substantial differences in physicochemical properties, potential reactivity, and possibly metabolism. 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 polyethylene glycol 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 polyethylene glycol 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 representative structures of the SOIs and the analogs that are among the PEGs cocamine and related ingredients are shown in red in these figures. 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 will 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:

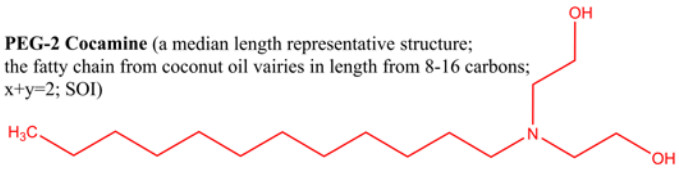


Figure 4. PEG-2 Cocamine (C12)

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

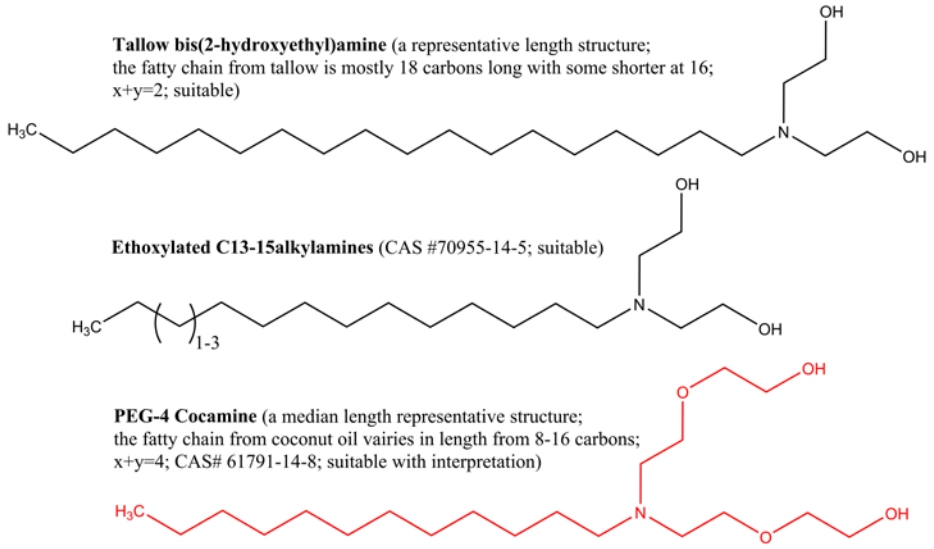


Figure 5. Analogs identified for PEG-2 cocamine

Tallow bis(2-hydroxyethyl)amine 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.

Ethoxylated C13-15 alkylamines 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 monoethoxylate 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.

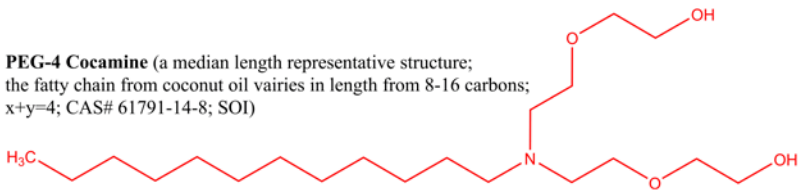


Figure 6. PEG-4 Cocamine (C12)

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

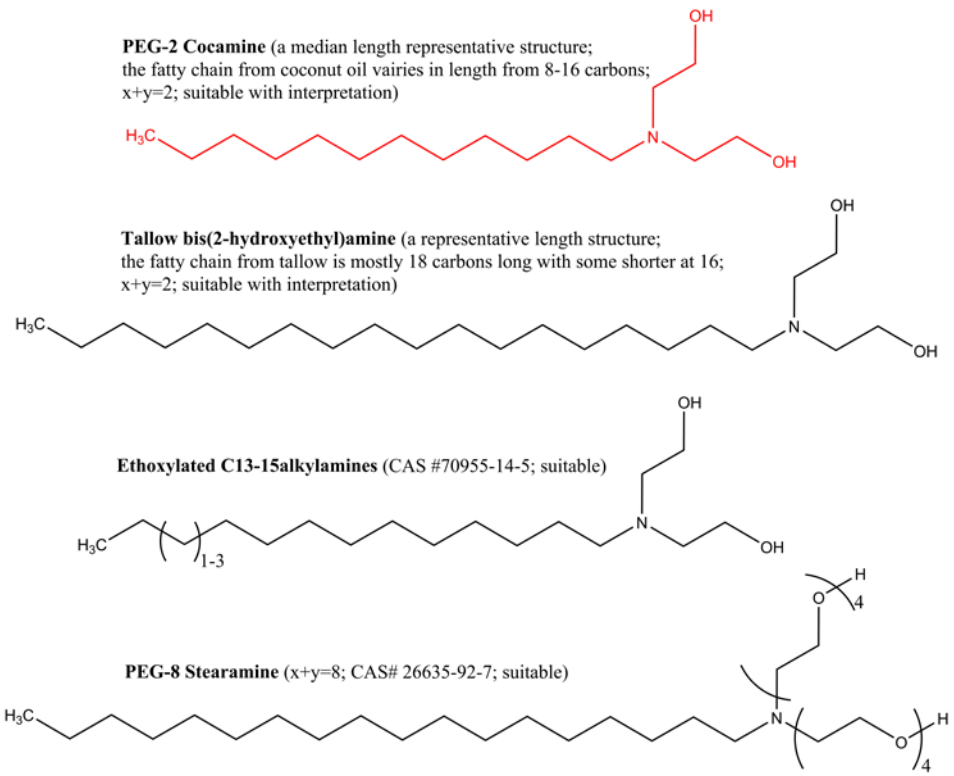


Figure 7. Analogs identified for PEG-4 cocamine

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

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

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

- The presence of monoethoxylate 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.

Ethoxylated C13-15 alkylamines is "suitable with interpretation" for PEG-4 cocamine because:

- The presence of monoethoxylate 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.

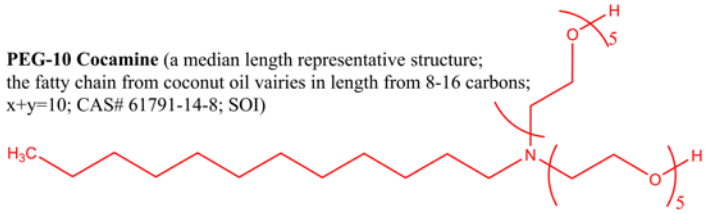


Figure 8. PEG-10 cocamine (C12)

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

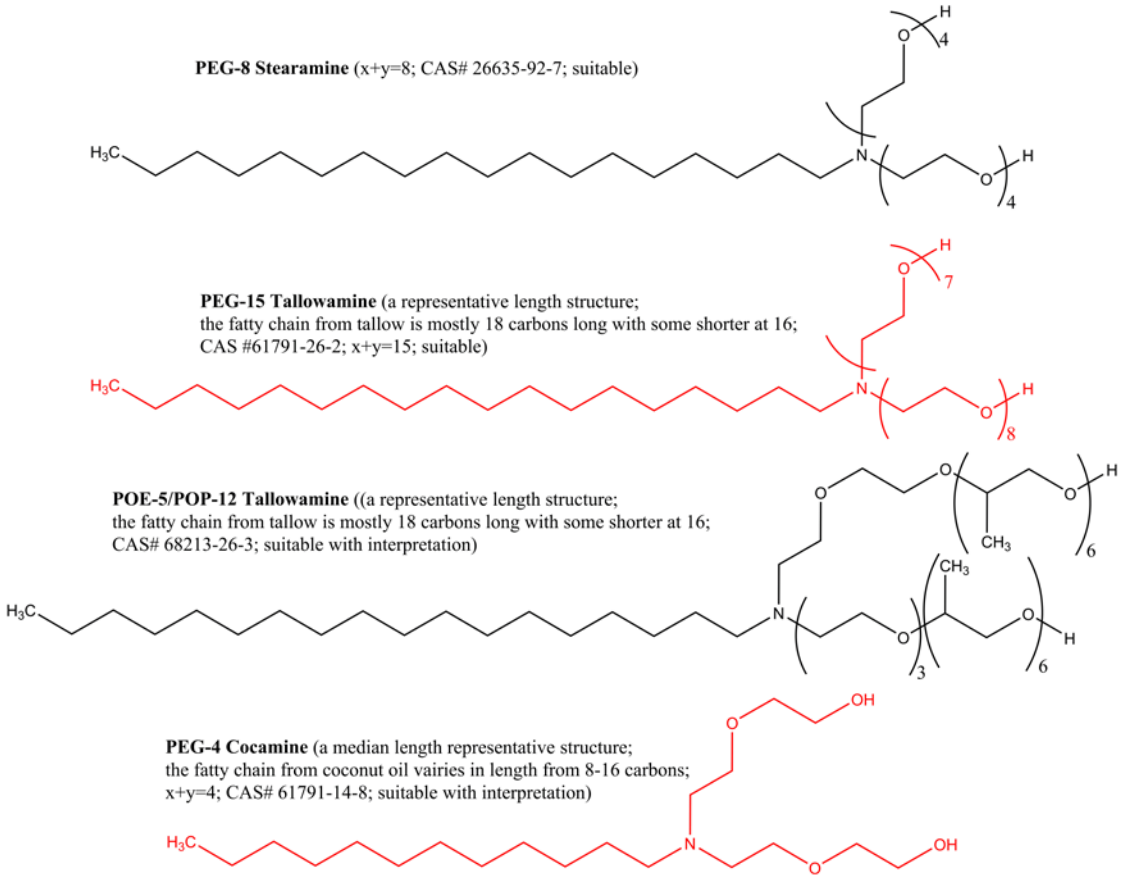


Figure 9. Analogs identified for PEG-10 cocamine

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.

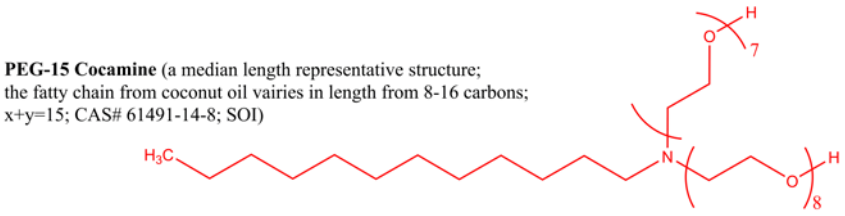


Figure 10. PEG-15 cocamine (C12)

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

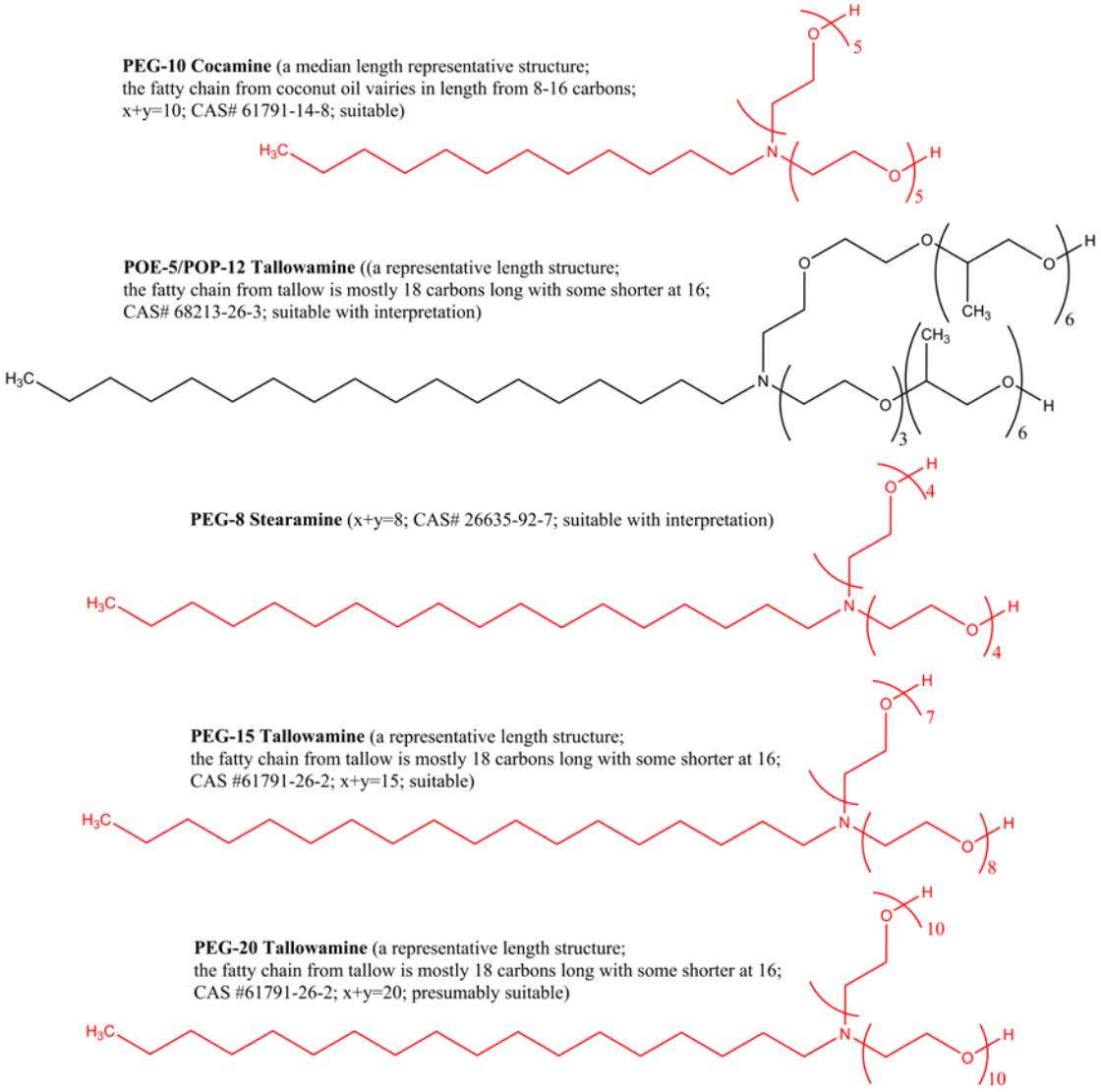


Figure 11. Analogs identified for PEG-15 cocamine

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® 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® 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." However, as the CIR SSC noted, the specificity of a "rapid prototype alert" is likely to be low. DEREK® does not reveal the structures of the proprietary ethylene glycol derivatives that led to the development of this rapid prototype alert.

DEREK® 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® knowledge base.

The CIR Expert 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.[17] 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, chain-length mix skews longer with tallow than with coconut oil. 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 monoethoxyl side chains (eg, the analog tallow bis(2- hydroxyethyl)amine; CAS# 61791-44-4) and others have polyethoxyl side chains (eg, the SOI PEG-4 cocamine; CAS# 61791-14-8), as shown in Figure 12.

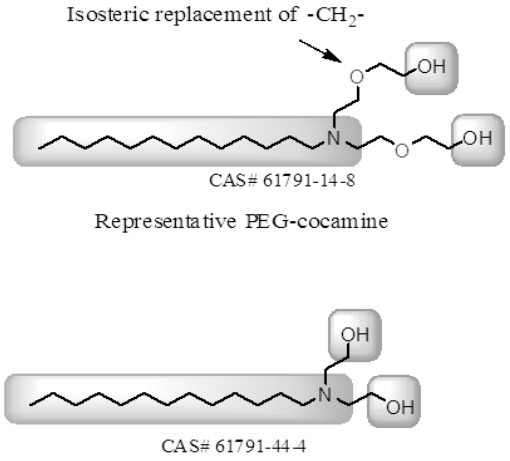


Figure 12. Isostericity of ether and methylene linkages

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.

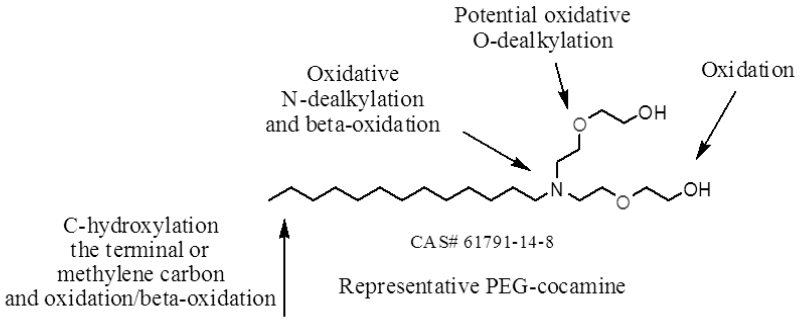


Figure 13. Theoretical metabolic transformations of PEGs cocamine ingredients.

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

The potential for *O*-dealkylation of 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.[37,38] 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).

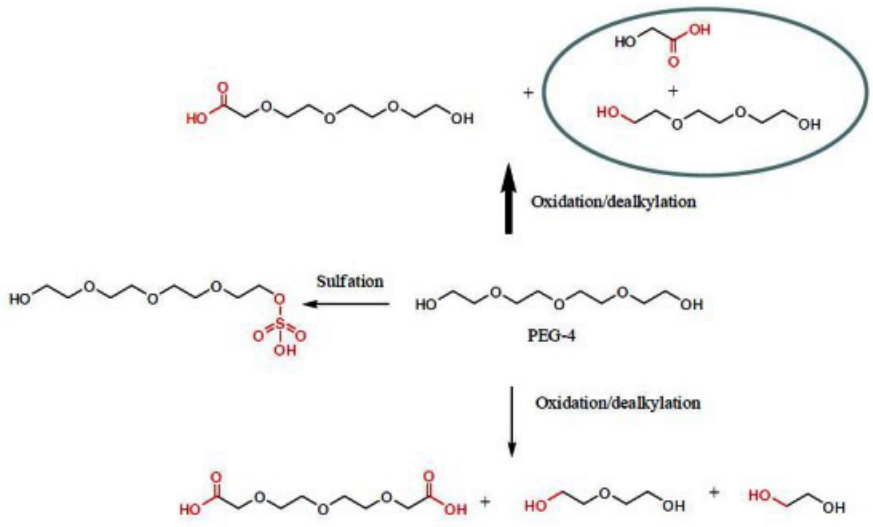


Figure 14. Metabolism of polyethylene glycols (PEGs)

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. PEGs-cocamine 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.

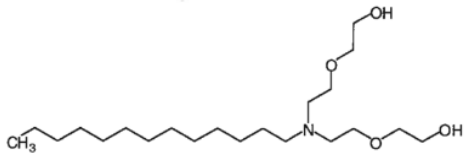


Figure 15. PEG-4 cocamine structure evaluated in the first case study.

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.

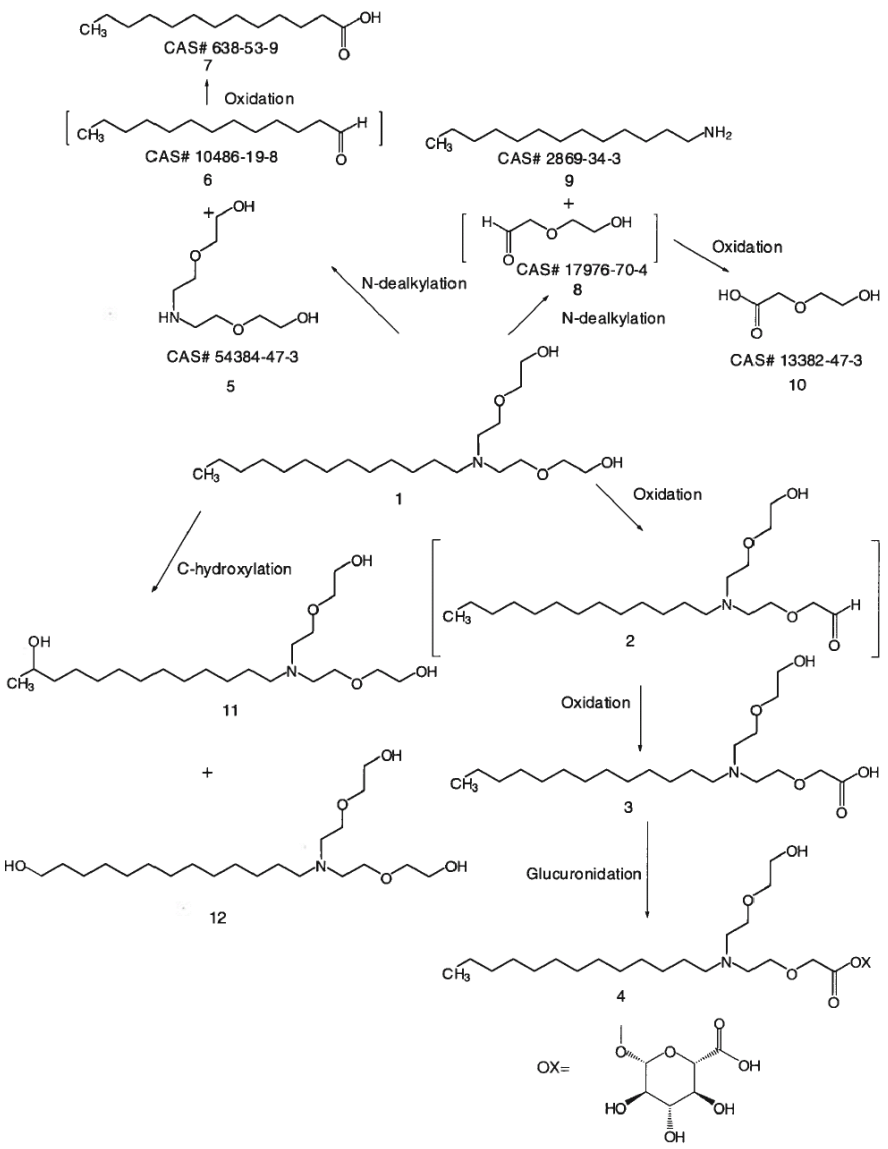


Figure 16. Predicted major metabolites of a PEG-4 cocamine in the first case study.

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

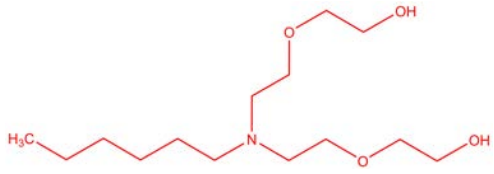


Figure 17. PEG-4 cocamine structure evaluated in the second case study.

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
-

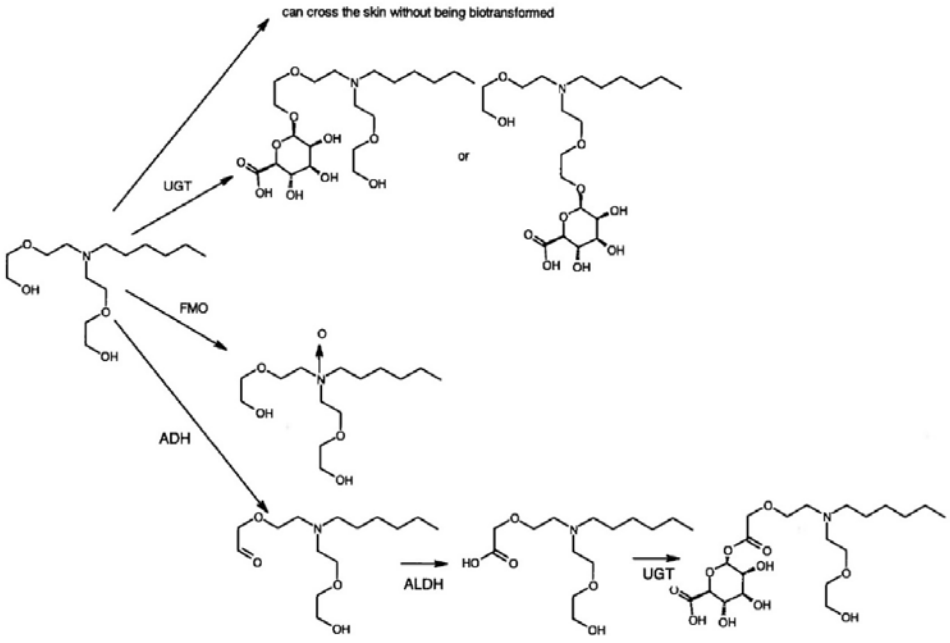


Figure 18. Plausible metabolism of a PEG-4 cocamine in the skin, from the second case study.

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

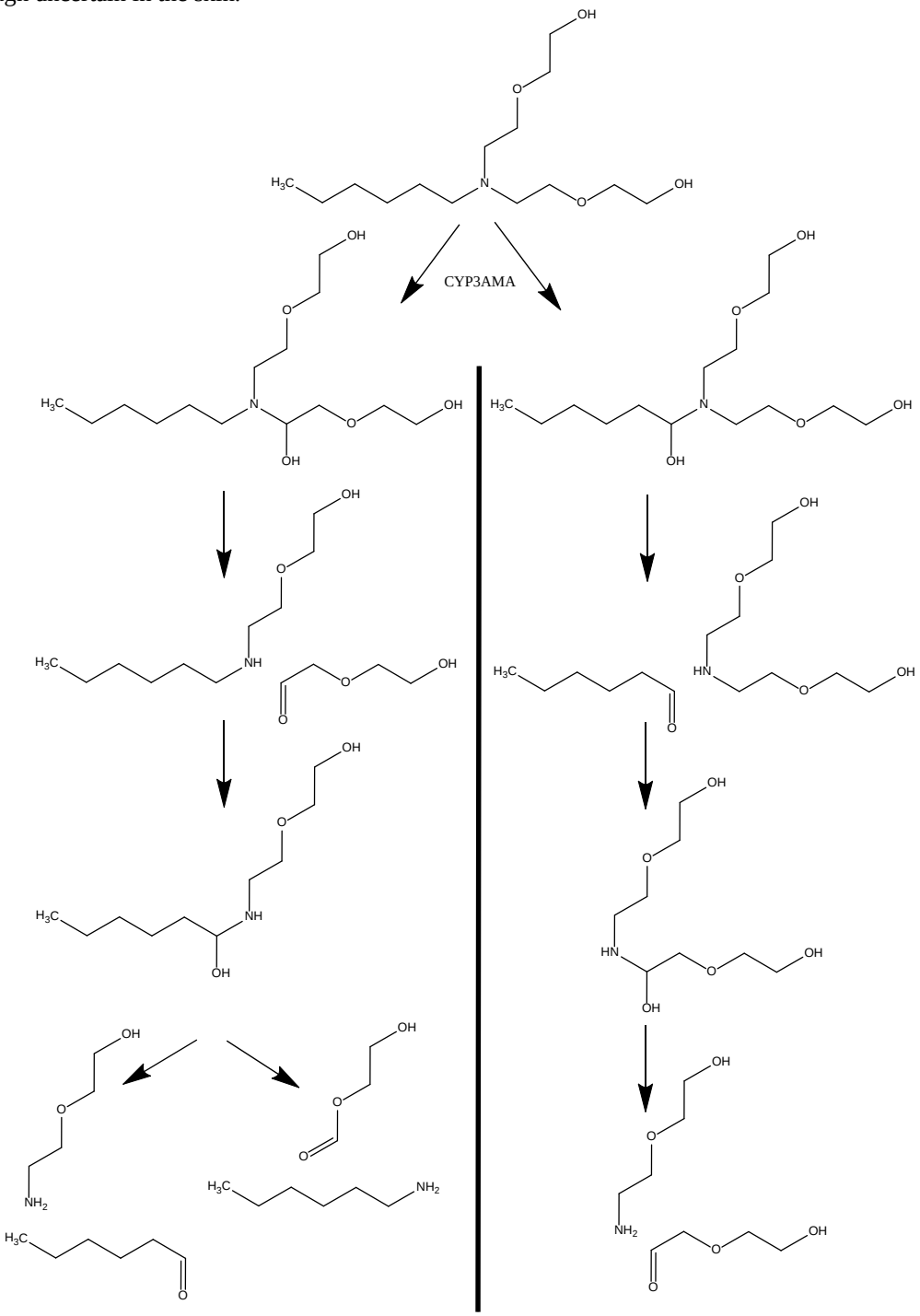


Figure 19. Possible *N*- or *O*-dealkylations in the skin (major in the liver).

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 10-13 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 address repeated-dose toxicity, genotoxicity, and DART as toxicological endpoints. Note that a rat DART screening test was identified for PEG-2 cocamine (Table 10).

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 tallow bis(2-hydroxyethyl) amine) (Tables 10 and 11) and x+y=15 to 17 (ie, two studies, each, for PEG-15 tallow amine and POE-5/POP-12 tallow amine) (Tables 12 and 13). In addition, a 90-day rat study and 90-day dog study on the analog ethoxylated C13-C15 alkylamines (x+y=2) were performed (Tables 10 and 11). 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 higher 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.[39-42] These lesions are attributable to the clearance of oils with high molecular weight, and are not associated with long-term effects."[40-42] 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]

Percutaneous Repeated-Dose Toxicity

Percutaneous 28-day repeated-dose toxicity studies have been conducted in rabbits with tallow bis(2-hydroxyethyl) amine (x+y= 2; one study; Tables 10 and 11) and PEG-20 tallow amine (x+y=20, two studies; Table 13). 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 10-13), including:

- Tallow bis(hydroxyethyl) amine C16-C18 (x+y=2); Tables 10 and 11
- PEG-8 hydrogenate tallow amine (x+y=8); Tables 11, 12 and 13
- PEG-15 tallow amine (x+y=15); Table 12
- PEG-20 tallow amine (x+y=20); Table 13

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 13). 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 13). The authors also noted that tallow bis(hydroxyethyl) amine C16-C18 (x+y=2) was negative in an *in vivo* mouse micronucleus assay (Tables 10 and 11).[5]

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

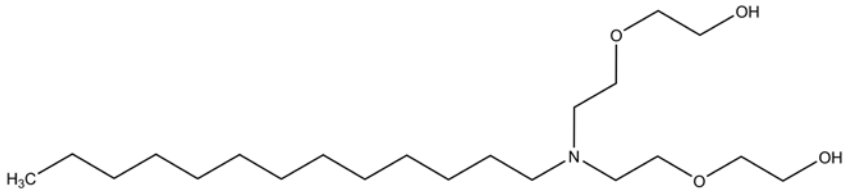


Figure 20. Structure of PEG-4 cocamine evaluated for genotoxicity and sensitization using computational models.

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® 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.[4,40] 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) Table 10
- PEG-15 tallow amine (x+y=15); Tables 12 and 13

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. [43] Hydroperoxides were the primary oxidation products formed.

The potential for peroxide formation in PEGs has been considered by the CIR Expert Panel, and some literature on the quantitation of peroxides in PEGs of various molecular weights has been cited in CIR safety assessment reports.[15,17] In the Amended Safety Assessment for triethylene glycol and polyethylene glycols (June 29, 2010), 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.[17]

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 structure activity (SAR) relationships, 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 monoethoxyl groups, rather than polyethoxyl, or one monoethoxyl group and one 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 length of the polyethylene glycol groups depend on the duration of the reaction, and these groups may not be symmetrical; typically, this reaction yields a range of polyethylene glycol 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. Aflatoxin contamination of raw and dried copra have been reported. Copra is the dried coconut kernels from which the fatty acids may be obtained to produce the PEGs cocamine.

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

VCRP and Industry survey data obtained in 2014 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 239 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 hydrogenated 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 hydrogenated 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.

As noted above, 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. The framework is a systematic, expert-driven method developed to identify and evaluate the suitability of analogs, based on similarities in chemical structure, reactivity, and metabolic and physicochemical properties, for use in read-across assessments. The framework is amenable to incorporating the results of (Q)SAR analyses to fill data gaps for specific endpoints or to inform the overall weight of evidence analysis that is integral to the exercise of the framework. The framework enables classifying candidate analogs in a manner that reflects the assumptions and uncertainties associated with their use in a safety assessment, based on structural, reactive, metabolic and physicochemical similarities to the SOI (ie, the chemical with missing toxicological data), and differences in physicochemical properties. The results include the classification of each candidate analog as suitable, suitable with interpretation, suitable with a precondition or not suitable. All of the relevant toxicological data available for the SOI and analogs classified as “suitable,” “suitable with interpretation” or “suitable with precondition” are then compiled and reviewed for consistency or concordance of toxicological responses and mechanisms or modes of action across multiple endpoints. All of the data are then taken together to develop an overall weight of evidence assessment, including a detailed review for consistency of the toxicology data for the analogs and the SOI, to develop a statement of confidence in the read-across assessment.

The framework performed well in a series of blinded case studies for all of the endpoints examined. The case studies showed that applying the framework can enable or facilitate the conduct of transparent, reproducible, and conservative read-across assessments. However, the successful application of the approach requires substantial expertise and discipline to avoid stepping over the boundaries of the defined analogs and the suitability rating system.

Four PEGs cocamine were selected as the structures of interest (SOIs) to cover the range of polyethylene glycol side-chain lengths for identifying analogs, including PEG-2 cocamine (Analog Group 1), PEG-4 cocamine (Analog Group 2), PEG-10 cocamine (Analog Group 3), and PEG-15 cocamine (Analog Group 4).

The analogs showed consistent biological responses, including the absence of genotoxicity and teratogenicity, 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 and, thus, inform the safety assessment of this ingredient group. For example, the potential for a representative structure of PEG-4 cocamine to induce dermal sensitization was

evaluated using predictive software. 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 as well as 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. Hydrogenated tallow will be saturated, but PEGs hydrogenated tallow amines will still have larger alkyl groups than the corresponding PEGs cocamine.

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." In previous safety assessments, the CIR Expert 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 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.

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 to some extent.

Another noteworthy difference among the SOIs and analogs is that some of them have monoethoxyl 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 monoethoxyl groups in 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 ethoxylated C13-C15 alkylamines, 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. 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. The potential differences in chemical reactivity, physicochemical properties, or metabolism of the analogs that 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 higher 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.

Percutaneous 28-day repeated-dose toxicity studies have been conducted in rabbits with tallow bis(2-hydroxyethyl) 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 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. There were no structural alerts for genotoxicity using the DEREK® system. PEG-4 cocamine was predicted to be non-mutagenic and to not be a precursor of chromosomal aberrations using the TIMES® model. The overall negative results of genotoxicity tests and computational predictions are consistent with the data reported in Appendix A of US EPA FND Amines Category HPV Chemical Challenge. 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 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

The Expert 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 32 of 47 ingredients addressed in this report. All of these 32 ingredients have $x+y > 5$, and they include PEGs cocamine, PEGs oleamine, PEGs tallow amine, PEGs hydrogenated tallow amine, PEGs soyamine, PEGs stearamine, and PEGs palmitamine.

In particular, the Panel agreed that gaps in genotoxicity and systemic toxicity data can be filled for these 32 ingredients 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.

The Panel noted that products containing these 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 assure the absence of a pathogenic agent in the ingredients, the PEGs tallow amine and PEGs hydrogenated tallow amine must be made from tallow containing a maximum level of insoluble impurities of 0.15% in 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 found that the information was insufficient to determine the safety of the 15 PEGs cocamine and related ingredients with $x+y \leq 5$, including PEG-2 rapeseedamine, PEG-2 lauramine, and others. They noted that each of these ingredients represents a distribution of molecules, some of which may be primary and secondary amines that may be glucuronidated or sulfated, and then undergo intramolecular cyclization to yield potentially sensitizing electrophilic quaternized intermediates. The prediction of metabolites using QSAR analysis of a single, idealized chemical structure for PEG-4 cocamine was not sufficient to address such possibilities. The additional data needed for these ingredients are:

(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. The Panel may assume 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 analogues 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 CIR Expert Panel concluded that the following 32 ingredients are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating:

PEG-8 cocamine*
PEG-10 cocamine*
PEG-12 cocamine*
PEG-15 cocamine
PEG-20 cocamine*
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-6 oleamine*
PEG-10 oleamine*
PEG-15 oleamine*
PEG-20 oleamine*
PEG-25 oleamine*
PEG-30 oleamine*
PEG-12 palmitamine*
PEG-8 soyamine*
PEG-10 soyamine*
PEG-15 soyamine*
PEG-10 stearamine*
PEG-15 stearamine*

PEG-50 stearamine*
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*

The CIR Expert Panel concluded that the available data are insufficient to make a determination that the following 15 ingredients are safe under the intended conditions of use:

PEG-2 cocamine
PEG-3 cocamine*
PEG-4 cocamine*
PEG-5 cocamine
PEG-2 hydrogenated tallow amine*
PEG-5 hydrogenated tallow amine
PEG-2 lauramine*
PEG-2 oleamine
PEG-5 oleamine*
PEG-2 rapseedamine
PEG-2 soyamine
PEG-5 soyamine
PEG-2 stearamine*
PEG-5 stearamine*
PEG-2 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]

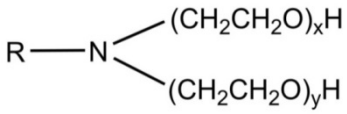
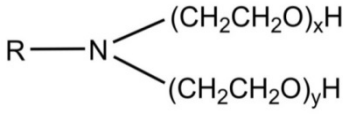
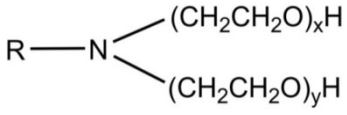
Ingredient CAS No.	Definition / Structure
PEG-2 cocamine 61791-14-8 (generic)	PEG-2 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene 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 2. 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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-3, -4, and -5 cocamine.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]
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 2. 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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-3 cocamine.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]
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 2. 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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-4 cocamine.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]

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

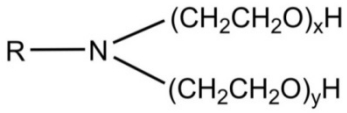
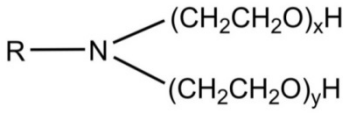
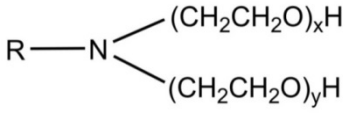
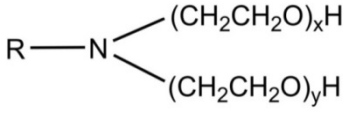
Ingredient CAS No.	Definition / Structure
PEG-5 cocamine 61791-14-8 (generic)	PEG-5 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene 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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 cocamine.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]
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 2. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]
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 2. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]
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 2. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]

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

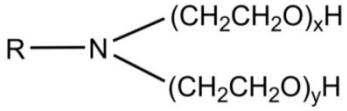
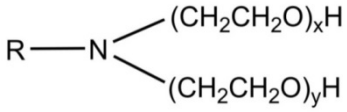
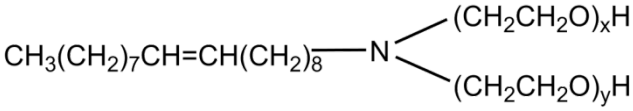
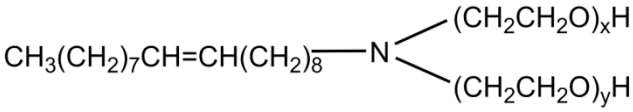
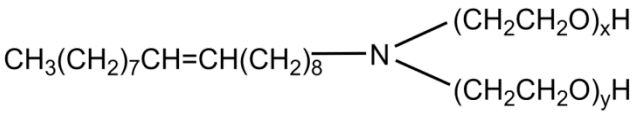
Ingredient CAS No.	Definition / Structure
PEG-15 cocamine 61791-14-8 (generic)	PEG-15 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  Where R represents the alkyl groups derived from the fatty acids of coconut oil and the x+y of the polyethylene 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 2. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]
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 2. Thus, each PEGs cocamine is a mixture of compounds with the major fatty-acid derived chain lengths of C12 to C14.][13] [The fatty chains in coconut oil vary from about 8 to 16 carbons long][4,44]
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2.][13]
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 oleamine.][13]
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.

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

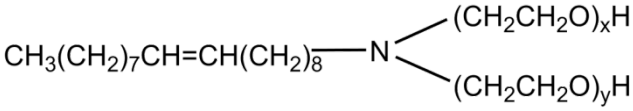
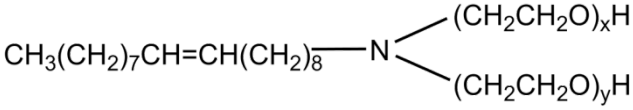
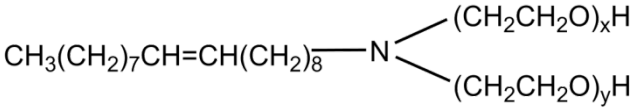
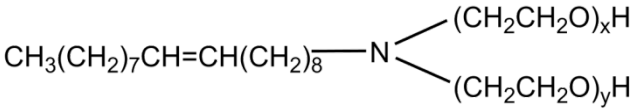
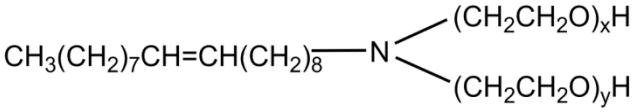
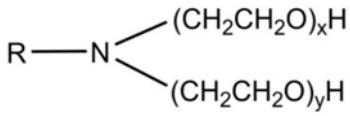
Ingredient CAS No.	Definition / Structure
PEG-10 oleamine 26635-93-8 (generic)	PEG-10 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 10.
PEG-15 oleamine 26635-93-8 (generic)	PEG-15 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x+y has an average value of 15.
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.
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.
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.
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 3. 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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2.][13] [The fatty chains in tallow vary from about 14 to 18 carbons long][4]

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

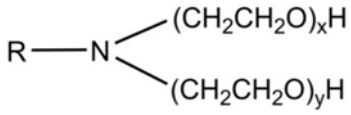
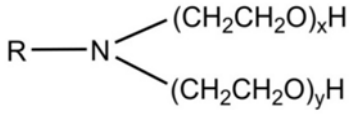
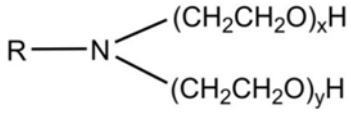
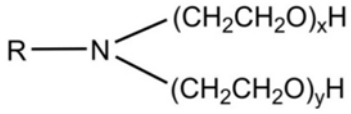
Ingredient CAS No.	Definition / Structure
PEG-7 tallow amine 61791-26-2 (generic)	PEG-7 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 7. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 3. 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]
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 3. 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]
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 3. 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]
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 3. 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]

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

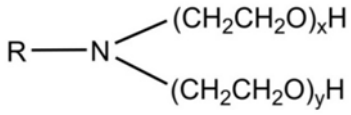
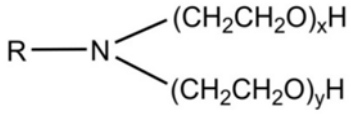
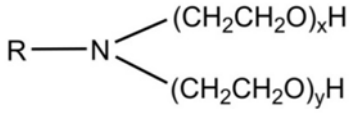
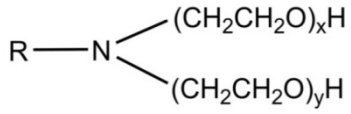
Ingredient CAS No.	Definition / Structure
PEG-22 tallow amine 61791-26-2 (generic)	PEG-22 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x+y has an average value of 22. [The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 3. 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]
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 3. 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]
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 3. 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]
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one 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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]

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

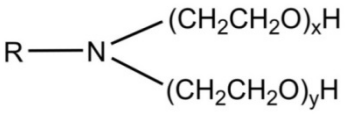
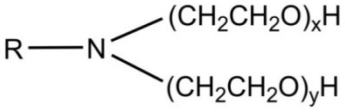
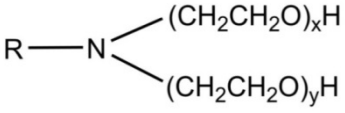
Ingredient CAS No.	Definition / Structure
PEG-5 hydrogenated tallow amine 61791-26-2 (generic)	PEG-5 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids 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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one 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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]
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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]
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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]

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

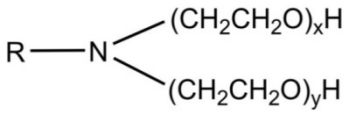
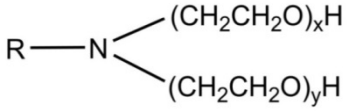
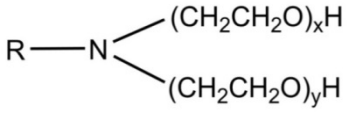
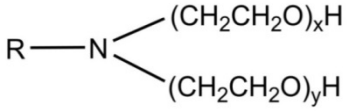
Ingredient CAS No.	Definition / Structure
PEG-15 hydrogenated tallow amine 61791-26-2 (generic)	PEG-15 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids 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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]
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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]
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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]
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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]

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

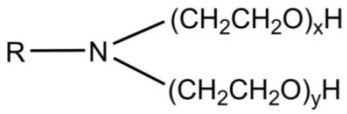
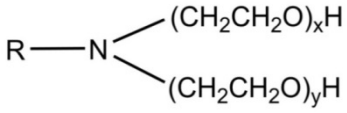
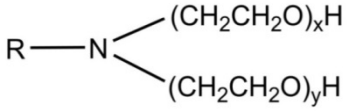
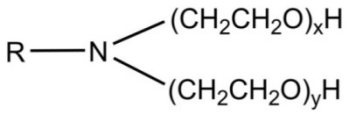
Ingredient CAS No.	Definition / Structure
PEG-50 hydrogenated tallow amine 61791-26-2 (generic)	PEG-50 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids 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.][13] [The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long][11,12,45]
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2..][13] [The fatty chains in soy oil are predominantly 18 carbons long][14]
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 soyamine.][13] [The fatty chains in soy oil are predominantly 18 carbons long][14]
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][14]

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

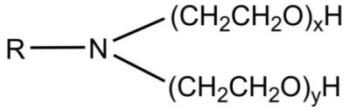
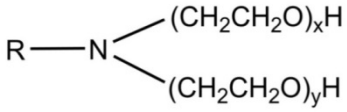
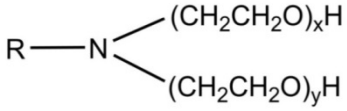
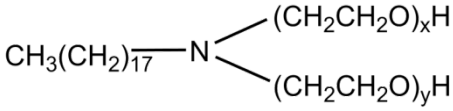
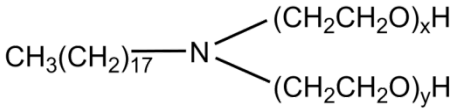
Ingredient CAS No.	Definition / Structure
PEG-10 soyamine 61791-24-0 (generic)	PEG-10 soyamine is a series of polyethylene glycol derivatives of soy acid that conform generally to the formula:  shown above, where R represents the alkyl groups derived from the fatty acids of soy and x+y has an average value of 10. [The fatty chains in soy oil are predominantly 18 carbons long][14]
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][14]
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2.][13] [The fatty chains in rapeseed oil are predominantly 16 to 22 carbons long][14,44]
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2.][13]
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2. The possibility of similar structural variations is notable for PEG-5 stearamine.][13]

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

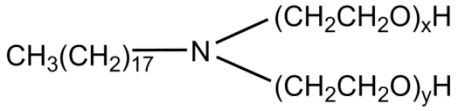
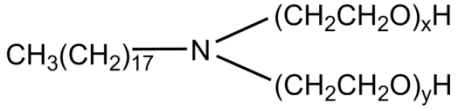
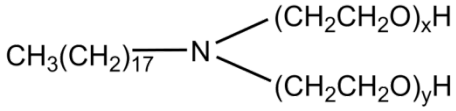
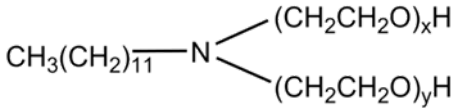
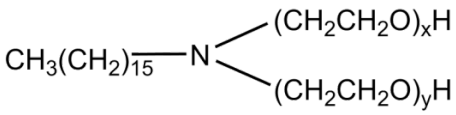
Ingredient CAS No.	Definition / Structure
PEG-10 stearamine 9003-93-4 (generic)	PEG-10 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x+y has an average value of 10.
PEG-15 stearamine 9003-93-4 (generic)	PEG-15 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x+y has an average value of 15.
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.
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 monoethoxyl groups, rather than polyethoxyl groups, if x and y both equal 1. The structure will have one monoethoxyl group and one polyethoxyl group if x=0 and y=2.][13]
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][44]

Table 2. Chain length distribution and degree of unsaturation of the fatty acids in coconut oil[4]

Fatty Acid Chain Length	Degree of Unsaturation	Composition
C6	None	0% to 1%
C8	None	5% to 9%
C10	None	5% to 10%
C12	None	44% to 53%
C14	None	13% to 19%
C16	None	8% to 11%
C18	None	1% to 3%
C16	1	0% to 1%
C18	1	5% to 8%
C18	2	1% to 3%

Table 3. 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 4. Chain length distribution and degree of unsaturation of the fatty acids in rapeseed oil[14]

Fatty Acid Chain Length	Degree of Unsaturation	Composition
C16	None	1.5% to 4.5%
C18	None	0.7% to 1.5%
C18	1	12.1% to 61.7%
C18	2	11.4% to 22.1%
C18	3	8.3% to 12.5%
C20	1	5.6% to 10.9%
C22	1	0.2% to 58.6%

Table 5. Chain length distribution and degree of unsaturation of the fatty acids in soybean oil[14]

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

Table 6. 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] / [16]
Color, (Gardner scale)	2.0 max. / 11.0 max.	[5] / [16]
Refractive Index @ 25 ºC	~1.466	[16]
pH (10% in IPA/H_2O)	9.0 to11.0	[5]
Amine Value	185 to 200	[16]
Secondary Amine (%)	0.5 max.	[18]
Primary & Secondary Amine (%)	5.0 max.	[16]
Tertiary Amine (%)	97.0 min. / 95.0 max. / 95 min. / 97 to 100	[5] / [16] / [46] / [18]
Nitrosamine (ppb)	50 max.	[18]
Moisture (%)	0.5 max. / 1.0 max. / Residual	[5] / [16] / [18]
Neutralization Eq.	290 to 310 / 280 to 303	[5] / [16]
PEG-5 Cocamine		
Physical Appearance	Yellow to amber liquid / Liquid @ 25ºC	[47] / [48]
Color, Gardner	12.0 max. / 7 max.	[47] / [48]
Specific Gravity @ 25ºC	0.976	[48]
Viscosity (kg/[s x m]) @ 20ºC	0.15	[48]
Vapor Pressure (mmHg) @ 20ºC	<0.1	[48]
Melting Point (ºC)	-9	[48]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[48]
pH (5% soln.)	9.0 to 11.0	[47]
Amine Value	128 to 138 / 129 to 137	[47] / [48]
Secondary Amine (%)	0.5 max.	[18]
Primary & Secondary Amine (%)	2 max.	[48]
Tertiary Amine (%)	96 min. / 95 min. / 97 to 100	[47] / [46] / [18]
Nitrosamine (ppb)	50 max.	[18]
Moisture (%)	1.0 max. / Residual / 1 max.	[47] / [18] / [48]
Neutralization Eq.	406 to 439 / 410 to 435	[47] / [48]
PEG-15 Cocamine		
Physical Appearance	Yellow to amber liquid	[5,49]
Color, Gardner	9.0 max. / 12 max.	[5] / [49]
pH (10% in IPA/H_2O / 5% soln.)	9.0 to 11.0 / 9 to 10.5	[5] / [49]
Amine Value	62 to 68	[49]
Tertiary Amine (%)	96 min.	[5,49]

Table 6. Supplier specifications and analytical data for PEGs cocamine and related ingredients

Moisture (%)	1.0 max.	[5,49]
Neutralization Eq.	825 to 905	[5,49]
PEG-2 Tallow Amine		
Physical Appearance	Liquid to semi-solid (paste) / Pale brown-yellow liquid / Paste @ 25ºC	[50] / [12,45] / [51]
Color, Gardner	8 max. / 6 max.	[50] / [51]
Average Molecular Weight (g/mol)	344 / 343	[12,45] / [11]
Specific Gravity @ 25ºC	0.916	[51]
Viscosity (kg/[s x m]) @ 50ºC	0.034	[51]
Vapor Pressure (mm Hg) @ 20ºC	<0.1	[51]
Melting Point (ºC)	29	[51]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[51]
Amine Value	156 to 165	[51]
Primary Amine (%)	0.4 / 0.8	[45] / [11]
Secondary Amine (%)	0.7 / 0.7	[45] / [11]
Primary & Secondary Amine (%)	1.2 / 1.5 / 3 max.	[12,45] / [11] / [51]
Tertiary Amine (%)	97.0 min. / 98.6 / 98.5 / 96	[50] / [12,45] / [11] / [51]
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	[12,45] / [11]
Moisture (%)	1.0 max.	[50]
Neutralization Eq.	350 to 370 / 340 to 360	[50] / [51]
PEG-5 Tallow Amine		
Physical Appearance	Clear liquid / Liquid-paste at 25ºC	[52] / [53]
Color, Gardner	8 max. / 7 max.	[52] / [53]
Specific Gravity @ 25ºC	0.950	[54]
Vapor Pressure (mmHg) @ 20ºC	<0.1	[54]
Melting Point (ºC)	12	[54]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[54]
pH (10% in IPA/H_2O)	9 to 11 / 11 to 11.6	[52] / [53]
Solubility (5% @ 20ºC)	Water, acetone, isopropanol, propylene glycol, xylene, ethanol	[54,55]
Amine Value	113 to 119	[54]
Primary & Secondary Amine (%)	2 max.	[54]
Tertiary Amine (%)	97 min. / 95 min. / 98 min.	[52] / [46] / [53]
Moisture (%)	1 max. / 1 max.	[52] / [53]

Table 6. Supplier specifications and analytical data for PEGs cocamine and related ingredients

Neutralization Eq.	475 to 495 / 470 to 495	[52] / [53]
PEG-15 Tallow Amine		
Physical Appearance	Clear liquid / Liquid-paste at 25ºC	[56] / [57]
Color, Gardner	8 max. / 8 max.	[56] / [57]
Specific Gravity @ 25ºC	1.024	[57]
Vapor Pressure (mmHg) @ 20ºC	<0.1	[57]
Melting Point (ºC)	-3	[57]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[57]
pH (5% soln.)	9 to 10.5 / 11 to 11.6	[56] / [57]
Solubility @ 25ºC	Water, acetone, isopropanol	[57]
Amine Value	59 to 63 / 59 to 63	[56] / [57]
Primary & Secondary Amine (%)	1 max.	[57]
Tertiary Amine (%)	97 min.	[56]
Moisture (%)	1.0 max. / 1 max.	[56] / [57]
Neutralization Eq.	890 to 951 / 890 to 950	[56] / [57]
PEG-2 Hydrogenated Tallow Amine		
Physical Appearance	Solid @ 25ºC	[58]
Color, Hazen	300 max.	[58]
Solubility @ 20ºC	Water, ethanol, propylene glycol	[58]
Density (kg/m^3) @ 50ºC	880	[58]
Viscosity (kg/[s x m]) @ 50ºC	0.042	[58]
Activity (%)	100	[58]
Tertiary Amine (%)	95 min. / 97 min.	[46] / [58]
Moisture (%)	1.0 max.	[58]
Neutralization Eq.	338 to 360	[58]
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 6. 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	[59]
Color (Gardner)	10 max.	[59]
Specific Gravity @ 25ºC	0.952	[59]
Vapor Pressure (mmHg) @ 20ºC	<1	[59]
Melting Point (ºC)	6	[59]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[59]
Amine Value (mgKOH/g)	113 to 119	[59]
Primary & Secondary Amine (%)	3 max.	[59]
Moisture (%)	1 max.	[59]
Neutralization Eq.	470 to 495	[59]
PEG-15 Soyamine		
Physical Appearance	Clear liquid at 25ºC	[60]
Color (Gardner)	10 max.	[60]
Specific Gravity @ 25ºC	1.023	[60]
Melting Point (ºC)	-8	[60]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[60]
pH	11.5	[60]
Amine Value	59 to 63	[60]
Primary & Secondary Amine (%)	1 max.	[60]
Moisture (%)	1 max.	[60]
Neutralization Eq.	895 to 955	[60]
PEG-5 Stearamine		
Physical Appearance @ 25 ºC	Yellow soft solid / Solid @ 25ºC	[61] / [62]
Color, (Gardner scale)	9 max. / 5 max.	[61] / [62]
Specific Gravity @ 60ºC	0.876	[62]
Viscosity (kg/[s x m]) @ 50ºC	0.068	[62]

Table 6. Supplier specifications and analytical data for PEGs cocamine and related ingredients

Vapor Pressure (mmHg) @ 25ºC	<0.1	[62]
Melting Point (ºC)	50	[62]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[62]
pH (5% soln.)	9.0 to10.0	[61]
Hydroxyl Number	210 to 240	[61]
Amine Value	110 to 120 / 150 to 160	[61] / [62]
Primary & Secondary Amine (%)	3 max.	[62]
Tertiary Amine (%)	97 min. / 95 min. / 97 min.	[61] / [46] / [62]
Moisture (%)	1.0 max.	[61] / [62]
Neutralization Eq.	470 to 510	[61]
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	[63]
Color, (Gardner scale)	8 max.	[63]
Specific Gravity @ 50ºC	1.015	[63]
Vapor Pressure (mmHg) @ 20ºC	<0.1	[63]
Melting Point (ºC)	9	[63]
Boiling Point (initial; ºC) @ 760 mm Hg	>300	[63]
pH	11 to 11.6	[63]
Amine Value	58 to 62	[63]
Primary & Secondary Amine (%)	1 max.	[63]
Moisture (%)	1 max.	[63]
Neutralization Eq.	900 to 960	[63]

Table 7. Current and historical frequency and concentration of use of PEGs cocamine according to duration and exposure.[2,19,20,64]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2014	**1996**	**2014**	**1995**	**2014**	**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

	2014	**1996**	**2014**	**1995**	**2014**	**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 7. Current and historical frequency and concentration of use of PEGs cocamine according to duration and exposure.[2,19,20,64]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2014	**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 8. Frequency (2014) and concentration of use (2014) according to duration and type of exposure for PEGs-Cocamine ingredients. [19,20,64]

	# 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**	**239**	**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	239	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. 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 10. 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.	9
Analogs							
PEG-2 tallow amine (aka ethanol, 2,2'-iminobis-,N-tallow alkyl derivatives)	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	8,11,12

Table 10. 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.
Ethoxylated C13-C15 alkylamines	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.		9
PEG-4 cocamine	61791-14-8	8-16	4	No data	No data	No data	-

Table 11. 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	9
PEG-2 tallow amine (aka ethanol, 2,2'-iminobis-,N-tallow alkyl derivatives)	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	8,11,12

Table 11. 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.
Ethoxylated C13-C15 alkylamines	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	9
PEG-8 stearamine	26635-92-7	16-18	8	Ames test: (-)	No data	No data	8,10

Table 12. 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	8,10
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.	9
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	9
PEG-4 cocamine	61791-14-8	8-16	4	No data	No data	No data	-

Table 13. 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	9
PEG-8 stearamine	26635-92-7	16-18	8	Ames test: (-)	No data	No data	8,10
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.	9
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	8

APPENDIX
FRAMEWORK FOR IDENTIFYING AND EVALUATING ANALOGS FOR READ ACROSS

The CIR SSC used the framework described below to evaluate and integrate data and the results of computational analyses for read-across assessments of the PEGs-cocamine ingredients.

The development of the framework was informed by the stepwise approach for analog read across proposed by the European Union (EU) Organisation for Economic Co-operation and Development (OECD) Guidance on Grouping of Chemicals (2007).[65] The steps include:

1. Identifying potential analogs
2. Gathering data on these potential analogs
3. Evaluating the adequacy of data for each potential analog
4. Constructing a matrix with available data for the target and analog(s)
5. Assessing the adequacy of the analog(s) to fill the data gap
6. Documenting the entire process

The guidance also emphasizes the importance of comparing the physicochemical properties of the analogs and the structure of interest (SOI) to be evaluated (eg, a cosmetic ingredient), and assessing the likely toxicokinetics of the analogs and the SOI, including the possibility that divergent metabolic pathways could be important.[65,66]

Using the OECD guidance as a foundation, a formal, systematic, comprehensive, expert-driven framework to identify, evaluate the suitability of, and select analogs, based on similarities in chemical structure, reactivity, and metabolic and physicochemical properties, was presented for use in read-across assessments.[3,67,68] The framework is amenable to incorporating the results of (Q)SAR analyses to fill data gaps for specific endpoints or to inform the overall weight-of-evidence analysis that is integral to the exercise of the framework.[3,65,67,68]

The framework was developed to facilitate the objective and reproducible selection of analogs, and enhances transparency in read-across assessments. The framework enables classifying candidate analogs in a manner that reflects the assumptions and uncertainties associated with their use in a safety assessment, based on structural, reactive, metabolic and physicochemical similarities to the SOI (ie, the chemical with missing toxicological data), and differences in physicochemical properties that could affect bioavailability and, consequently, the biological responses that can be expected *in vitro* or *in vivo*.

The framework includes a decision tree that depicts the series of questions that a medicinal chemist addresses about the similarities of a candidate analog and an SOI in structure, reactivity, metabolism, and physicochemical properties.[3] The result of applying the decision tree typically yields a series of "pre-ranked" analogs that are presented to the toxicologists for the read-across assessment.

The results include the classification of each candidate analog as (1) suitable, (2) suitable with interpretation, (3) suitable with a precondition or (4) not suitable:

1. Analogs categorized as "suitable" have the same functional groups, core structure and prevalence and location of reactivity-modifying double bonds as the SOI
2. Analogs categorized as "suitable with interpretation" have the most salient features relevant for reactivity and toxicological activity in common with the SOI, but have other characteristics that differ (ie, primarily differing physicochemical properties), but these differences do not affect reactivity or do not lead to metabolic divergence that could result in different toxicological profiles
3. Analogs categorized as "suitable with precondition" typically require a hydrolytic or enzymatic reaction to yield the SOI or a close analog.
4. Structures considered, categorized as unsuitable, and not used for read across to the SOI

In addition, the outcome includes a qualitative characterization of (1) the strength of the evidence supporting the hypothesis of similarity between each candidate analog and the SOI, and (2) the uncertainties associated with the use of the analogs selected for read across.

An important element of the framework is the emphasis on evaluating the potential that an analog and the SOI could show toxicologically significant metabolic convergence or divergence. The search for analogs begins with analysis of key structural or substructural features and functional groups of the SOI and its likely metabolites. Metabolic pathways and major metabolites are identified based on a review of published information or on predictive software.[3]

The authors have also developed a promising battery of models to evaluate the potential of chemicals to cause developmental and reproductive toxicity (DART), including an empirically-based decision tree informed by the principles of estrogen-receptor interactions combined with the CEASAR model.[67,68] This tool was designed to serve as another important element in the overall weight-of-evidence analyses conducted using the framework.

Searching for candidate analogs using the framework requires databases that support substructure and structure similarity searches and facilitate the identification of similar structures for which there are relevant toxicological data (eg, AMBIT®,

ChemIDPlus®, Scifinder®, The OECD Toolbox, and DSSTox).[3] Each candidate analog is then compared to the SOI to identify features that could affect toxicity, including:

- Common structural alerts (eg, using DEREK® software)
- Key functional groups (eg, ester, aldehyde, amide, or amine)
- Core structures (eg, phenyl ring, alkyl chain, double bonds conjugated or positioned close to functional groups)
- Differences in physicochemical properties (eg, molecular weight, pK_a, log P, log D and solubility estimated using ACD/Labs® property estimation software)

Evaluating the potential for the metabolism of the analog and the SOI to diverge is accomplished using combinations of metabolism databases (eg, DiscoveryGate® or Metabolism®), scientific literature searches, substructure searches, software prediction tools (eg, METEOR®), *in vitro* test results, and the expert judgment of a medicinal chemist.

All of the relevant toxicological data available for the SOI and analogs classified as "suitable," "suitable with interpretation" or "suitable with precondition" are then compiled and reviewed by toxicologists for consistency or concordance of toxicological responses and mechanisms and/or modes of action across multiple endpoints.[3,65]

If a candidate analog has a different toxicity profile than the other candidate analogs, then a well-documented, clear rationale for why that chemical does not fit is needed before moving forward with the read-across assessment; otherwise, more data will be needed to support a decision to move forward with an analysis more likely to have an acceptable degree of uncertainty.

Corroborating data on the SOI may be available to consider for one or more toxicological endpoints. For example, toxicity data may be missing for the SOI for one toxicological endpoint, but data for the SOI for other endpoints may serve as "anchor data" to compare with the corresponding data available for the analog(s). Confidence in the selection of analogs can also be bolstered by knowledge of the molecular mechanism(s), mode(s) of action, or adverse outcome pathway(s) of analogs that can be toxic. The number and the suitability of the analogs that can be identified to evaluate the SOI, and the quality of the study data on the analogs, are other important factors to consider when characterizing the uncertainty associated with a read-across assessment.

The outcome of the classification of the analogs and the integrated review of the analog toxicology data enables a transparent characterization of the uncertainty associated with using the analogs to conduct a read-across assessment of the SOI.[67]

Uncertainty Rankings

High Uncertainty	Moderate Uncertainty	Low Uncertainty
Read across not recommended	Read across may be possible for some endpoints – larger margin of exposure required	Read across does not require a larger margin of exposure

All of the data are taken together to develop an overall weight-of-evidence assessment, including a detailed review for consistency of the toxicology data for the analogs and the SOI, to develop a statement of confidence in the read-across assessment. Exercising the framework can identify multiple analogs of similar suitability for a SOI.

If the weight of evidence supports the use of these analogs for read across, then the most toxic ("worst-case") analog for each hazard endpoint can be identified to enable selecting the critical effect and the point of departure (POD), such as a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL), for the rest of the safety assessment.[3]

In a series of blinded case studies of diverse SOIs, the framework performed well for the endpoints examined (genotoxicity, repeated-dose toxicity, developmental toxicity, and reproductive toxicity).[67,68] Estimates of PODs in the case studies were comparable to conservative PODs that had been independently derived from toxicity data by regulatory and advisory agencies.[67] Predictions of 14 blinded case studies were:

- Genotoxicity (+/-); All correct predictions
- Repeated-dose toxicity (surrogate NOAEL estimates); No underestimates
- Developmental toxicity (critical effect +/-; if +, surrogate NOAEL estimates); No underestimates
- Reproductive toxicity (critical effect +/-; if +, surrogate NOAEL estimates); No underestimates

The read-across results were protective compared to *bona fide* toxicity data on the case-study chemicals. The authors concluded that the process can be successfully applied to develop surrogate toxicity values for safety assessments.[4,5] However, Dr. Blackburn emphasized that the successful application of the approach requires substantial expertise and discipline to avoid stepping over the boundaries of the defined analogs and the suitability rating system.

In sum, the case studies showed that applying the framework can enable or facilitate the conduct of transparent, reproducible, and conservative read-across assessments.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: October 31, 2014

SUBJECT: Requested Studies to Support the Safety of PEG Cocamine Ingredients

Salmonella/Mammalian Microsome Mutagenesis Assay (Ames Test) Study No. 003-407-637-1, EG&G Mason Research Institute. March 31, 1981

Week Oral (Dietary) Toxicity Study in the Rat ECM BTS 306, E1095.01. Hazleton Laboratories Europe LTD. February 1982

E1069.02: A 4 Week Percutaneous Toxicity Study in the Rabbit, ECM BTS 306 ET Base. Hazleton Laboratories Europe LTD. December 1981

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SALMONELLA/MAMMALIAN MICROSOME MUTAGENESIS ASSAY

(Ames Test)

PEG-8 Stearamine

Sponsor: [redacted]

[redacted]

Study No.: 003-407-637-1
Test Article I.D.: E1023.01
Test Article Lot No.: 1
Test Article Description: Brown, Non-viscous Liquid
Storage Conditions: Room Temperature
Date Received: 3/17/81
Date Study Started: 3/18/81
Date Study Completed: 3/31/81
Report Date: 3/31/81

Study Coordinator: [redacted]

Study Director: Steve R. Haworth, Ph.D.
EG&G Mason Research Institute

Steve R. Haworth 3/31/81
Steve R. Haworth, Ph.D. Date
Study Director

[redacted]

[redacted]

EG&G MASON RESEARCH INSTITUTE
1530 EAST JEFFERSON STREET, ROCKVILLE, MARYLAND 20852 • TEL. (301) 770-4400

QUALITY ASSURANCE UNIT STATEMENT

The Salmonella/Mammalian-Microsome Plate Incorporation Mutagenesis Assay has been divided into a series of critical phases. Using a random sampling approach, the QAU monitors each of these in process phases over a series of studies. It examines procedures, documentation, equipment, etc. to assure that the test is conducted according to the protocol and in compliance with the Good Laboratory Practice Regulations. Findings are reported to the study director on the day of each inspection and on the day of the review of the final report.

The following are the inspection dates, critical phases inspected, and report dates of QAU monitors of the Salmonella/Mammalian-Microsome Plate Incorporation Mutagenesis Assay of Study No.: 003-407-637-1; E1023.01.

DATE OF INSPECTION	CRITICAL PHASES INSPECTED	REPORT SUBMITTED TO MANAGEMENT
3/18/81	Initial toxicity: Strain characterization Dilution of test article Treatment & plating of the cultures	3/27/81
3/20/81	Strain characterization Treatment & plating of the cultures	3/27/81

The final report was reviewed for compliance with the GLP's on March 30, 1981.

Nona S. Karten
QAU Manager

3/31/81
Date

Introduction

[redacted] test article E1023.01 [redacted] was received on March 17, 1981, for testing in the Salmonella/mammalian-microsome mutagenicity assay using five tester strains, TA98, TA100, TA1535, TA1537 and TA1538, both with and without metabolic activation by Aroclor induced rat liver microsomes.

Materials and Methods

The experimental protocol (see Appendix) is a modification of that described by Ames, B. N., et al. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutation Research 31:347-364, 1975.

Conclusions

The results of the Salmonella/mammalian-microsome mutagenicity assay indicate that [redacted] test article [redacted] did not cause a significant increase in the number of revertants per plate of any of the tester strains with or without metabolic activation by Aroclor induced rat liver microsomes.

Note: 1. All of the raw data generated by the assay and the original final report will be maintained in EG&G Mason Research Institute's archives located in our Rockville, Maryland facilities.

2. The stability of the test article under the actual experimental conditions used in this study was not determined by EG&G Mason.

All test article stock solutions were freshly prepared immediately before their use in each procedure.

RESULTS

EG&G MASON RESEARCH INSTITUTE

Preliminary Toxicity Determination
of Test Article

637 - A1
Experiment Number

003-407-637-1
Study Number

ZI023.01
Test Article Identification

Table 1

Test Compound Concentration µl/Plate	TA100 Viable Count/ Plate	TA100 Revertants/ Plate	TA100 Background Bacterial Lawn
50 µl H2O	210	80	* 1
100 µl H2O	367	103	1
0.003	320	74	1
0.01	350	68	1
0.03	166	102	1
0.1	11	37	3
0.3	7	0	4
1.0	6	12	5
3.1	4	0	5
10.0	8	0	5
20.0	3	0	5
40.0	3	0	5

Date Plated 3/18/81

* See Key on the Following Page

Colonies were machine Counted

Eight serial half-log dilutions of the test compound are plated with TA100 on minimal agar plus 10XSA and on minimal agar plus 1XSA. Equal numbers of cells are seeded on each plate in the presence of the test compound. The percent survival of an appropriately diluted TA100 culture on the 10XSA supplemented plates is determined by comparing numbers of colonies on the solvent control with those on the plates containing test compound. Toxicity on the 1XSA supplemented plates is detectable by a decrease in the number of revertant colonies occurring per plate and by a thinning or disappearance of the background bacterial lawn.

Form No. WL-162
5/5/80

Condition of the Background Bacterial Lawn

The condition of the background bacterial lawn is evaluated for each plate in the spontaneous/induced revertant series, both macroscopically and microscopically by using a dissecting microscope. The evaluation is recorded using the following code:

1. Normal - distinguished by a healthy microcolony lawn.

2. Slightly Reduced - distinguished by a noticeable thinning of the microcolony lawn compared to that of the solvent control plate.

3. Moderately Reduced - distinguished by a marked thinning of the microcolony lawn and an increase in the size of the microcolonies compared to the solvent control plate.

4. Extremely Reduced - distinguished by an extreme thinning of the background microcolony lawn, and a large increase in the size of the microcolonies compared to the solvent control plate.

5. Absent - distinguished by a complete lack of any microcolony background lawn.

Evidence of precipitate on the spontaneous/induced revertant plates is recorded by addition of the following precipitate code to the code number used to evaluate the condition of the background bacterial lawn.

SP - Slight Precipitate - distinguished by noticeable precipitate on the plate, but the precipitate does not influence counting of the plate.

MP - Moderate Precipitate - distinguished by a marked amount of precipitate on the plate, requiring the plate to be hand counted.

HP - Heavy Precipitate - distinguished by a large amount of precipitate on the plate, making the required hand count difficult.

Thus, 3MP would identify a spontaneous/induced revertant plate with a moderately reduced background bacterial lawn with a marked amount of precipitate which required a hand count.

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SALMONELLA [illegible] ASSAY

[illegible]

003-407-637-1 Study Number	E1023.01 Test Article Identification	0.0008 µl - 0.08 µl Dose Range

637-B1 Experiment Number

		Solvent H_2O 50 µl	Concentration (µl per plate) 0.0008	0.004	0.02	0.04	0.08		
Strain: TA98 Date Plated: 3/20/81 No. of Cells Seeded: 0.9 x10^8 Metabolic Activation: Rat Liver Colonies were manually counted	Revertants per Plate	33	38	27	32	25	36		
		24	34	31	28	33	40		
		28	28	27	33	26	28		
	Averaged Revertants	28	33	28	31	28	35		
	Standard Deviation	5	5	2	3	4	6		
Strain: TA98 Date Plated: 3/20/81 No. of Cells Seeded: 0.9 x10^8 Metabolic Activation: None Colonies were manually counted	Revertants per Plate	15	24	25	25	19	9		
		19	16	30	30	22	15		
		29	27	20	24	25	23		
	Averaged Revertants	21	22	25	26	22	16		
	Standard Deviation	7	6	5	3	3	7		

Form No. WL-160
5/5/80

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SALMONELLA MUTAGENESIS ASSAY

003-97-637-1
Study Number

E1023.01
Test Article Identification

0.0008 µl - 0.08 µl
Dose Range

637-B1
Experiment Number

		Solvent H2O 50 µl	Concentration (µl per plate) 0.0008	0.004	0.02	0.04	0.08		
Strain: TA100 Date Plated: 3/20/81 No. of Cells Seeded: 1.2 x10^8 Metabolic Activation: Rat Liver Colonies were machine counted	Revertants per Plate	156	134	156	136	169	149		
		149	105	133	141	131	121		
		134	133	153	119	108	145		
	Averaged Revertants	146	124	147	132	136	138		
	Standard Deviation	11	16	13	12	31	15		
Strain: TA100 Date Plated: 3/2/81 No. of Cells Seeded: 1.2 x10^8 Metabolic Activation: None Colonies were machine counted	Revertants per Plate	150	133	130	142	127	84		
		131	125	128	118	145	71		
		119	138	138	155	121	47		
	Averaged Revertants	133	132	129	138	131	67		
	Standard Deviation	16	7	10	19	12	19		

Form No. WL-160
5/5/80

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SALMONELLA MUTAGENESIS ASSAY
Page 4

003-407-637-1 Study Number	B1023.01 Test Article Identification	0.0008 µl - 0.08 µl Dose Range

637-B1
Experiment Number

		Solvent 50 µl	Concentration (µl per plate) 0.0008	0.004	0.02	0.04	0.08		
Strain: TA1535 Date Plated: 3/20/81 No. of Cells Seeded: 1.0 x10^8 Metabolic Activation: Rat Liver Colonies were manually counted	Revertants per Plate	17	15	14	12	9	17		
		14	11	11	7	13	16		
		19	12	12	19	12	17		
	Averaged Revertants	17	13	12	13	11	17		
	Standard Deviation	3	2	2	6	2	1		
Strain: TA1535 Date Plated: 3/20/81 No. of Cells Seeded: 1.0 x10^8 Metabolic Activation: None Colonies were manually counted	Revertants per Plate	16	24	30	22	19	18		
		16	25	22	21	20	16		
		24	24	25	28	20	19		
	Averaged Revertants	22	24	26	24	20	18		
	Standard Deviation	5	1	4	4	1	2		

Form No. WL-160
5/5/80

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SALMONELLA MUTAGENESIS ASSAY

Table 5

003-407-637-1	E1023.1	0.0008 µl - 0.08 µl
Study Number	Test Article Identification	Dose Range

637-B1
Experiment Number

		Solvent DMSO 50 µl	Concentration (µl per plate) 0.0008	0.004	0.02	0.04	0.08		
Strain: TA1537 Date Plated: 3/20/81 No. of Cells Seeded: 1.1 x10^8 Metabolic Activation: Rat Liver Colonies were manually counted	Revertants per Plate	5	11	6	13	14	9		
		10	15	11	13	5	8		
		9	11	5	4	15	8		
	Averaged Revertants	8	12	7	10	11	8		
	Standard Deviation	3	2	3	5	6	1		
Strain: TA1537 Date Plated: 3/20/81 No. of Cells Seeded: 1.1 x10^8 Metabolic Activation: None Colonies were manually counted	Revertants per Plate	9	7	3	10	13	3		
		6	5	10	7	7	4		
		5	5	8	9	5	4		
	Averaged Revertants	7	6	7	8	8	4		
	Standard Deviation	2	1	4	2	4	1		

Form No. WL-160
5/5/80

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SALMONELLA MUTAGENESIS ASSAY

Tab 6

003-4 7-637-1
Study Number

B1023
Test Article Identification

0.0008 µl - 0.08 µl
Dose Range

637-B1
Experiment Number

		Solvent H_2O 50 µl	Concentration (µl per plate) 0.0008	0.004	0.02	0.04	0.08		
Strain: TA1538 Date Plated: 3/20/81 No. of Cells Seeded: 0.9 x10^8 Metabolic Activation: Rat Liver Colonies were manually counted	Revertants per Plate	14	17	10	14	9	26		
		16	16	14	13	12	16		
		21	20	20	14	17	19		
	Averaged Revertants	17	18	15	14	13	20		
	Standard Deviation	4	2	5	1	4	5		
Strain: TA1538 Date Plated: 3/20/81 No. of Cells Seeded: 0.9 x10^8 Metabolic Activation: None Colonies were manually counted	Revertants per Plate	14	5	7	8	4	5		
		7	13	13	8	7	8		
		10	8	9	5	5	1		
	Averaged Revertants	10	9	10	7	5	5		
	Standard Deviation	4	4	3	2	2	4		

Form No. WL-160
5/5/80

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SALMONELLA MUTAGENESIS ASSAY

Positive Controls

Table

003-40[illegible]-1
Study Number

637-B1
Experiment Number

E1023.01
Test Article Identification

Date Plated	Strain	Chemical	Concentration per plate	Metabolic Activation	Revertants/Plate			Averaged Revertants per plate	S.D.
3/20/81	TA98	2-Aminoanthracene	1.0 µg	Rat Liver	501	562	421	495	71
3/20/81	TA98	2-Nitrofluorene	10.0 µg	None	1119	1126	1010	1085	65
3/20/81	TA100	2-Aminoanthracene	1.0 µg	Rat Liver	1206	1123	1354	1228	117
3/20/81	TA100	1,3-Propane Sultone	0.04 µl	None	830	784	985	866	105
3/20/81	TA1535	1,3-Propane Sultone	0.04 µl	None	1219	1144	1208	1190	41
3/20/81	TA1537	9-Aminoacridine	75 µg	None	1935	1893	1383	1737	307
3/20/81	TA1538	2-Nitrofluorene	10.0 µg	None	1950	1908	1634	1831	172

Form No. WL-161
5/5/80

Colonies were machine counted

TEST SUBSTANCE CHARACTERISATION REPORT

[redacted]

A

Test Substance Identification Number E- 1023.01

[redacted]

B

Name of Product or Ingredient (or code designation) Genamin S080 (20 % in water + H_3PO_4)

[redacted]

Physical Form Liquid Colour Brownish Density 0.99

Solubility Water pH (conc) 4.0 Sample Expiration Date

Recommended Storage Conditions Ambient

Hazards (i.e. flammability, toxic gases)

C

FORMULATED COMPOSITION

	Nominal Level (% by Wt)	Acceptable Range (b)	Stock Code No.	Supplier	Lot Number (b)
Alkylamineethoxylate : (Alkyl = Stearic) (EO = 8) Alkyl = C_{14} 5 % C_{16} 30 % C_{18} 65 % Density 0.88 gr./cm^3 (50°C)	99.5 %			Genamin S080 - Hoechst	E - 10346 P86 EIC E-3399 Rec'd Jan.26, '81
20 % solution : - Genamin S080	20.00 %				
- Phosph. Acid (85 %)	3.57 %				
- Dist. water	76.43 %				
	100.00 %				

(a) Ingredients will be listed by chemical name; non-chemical names such as Tergitol 15-3-5 or Yellow Dye D&C No. 10 may be acceptable but should be previewed with the responsible toxicologist. Chemical names which are inconveniently long may be abbreviated in tables but should be listed in full in referenced footnotes. Non-definitive identifications (e.g. Arquad, BC-base) are not acceptable).

(b) If information requested is not known then the symbol NK will be entered.

[redacted]

D

ISCR ANALYTICAL REQUEST FORM

Please carry out the following analyses according to your recorded procedures. This data is needed for non-clinical safety studies.

Sign [redacted] Date 6 Feb. '81

Agreed for Analytical Section [redacted] Date

Agreed for Human Safety [redacted] Date

Date Submitted	Submitter Code	Component or Property	Measured Value	Analytical Notebook Ref
Feb. 6, '81	- OEB 167 (Genamin S080 Raw Material)	- Cat. SO_3	12.74 %	
		- Amines Prim.	0.02	
		Sec.	0.00	
		Tertiary	1.59 %	
		- N_2	2.17 %	
	- OEB 192 (20 % solution)	- Cat. SO_3		
		- pH		

[redacted] (signature) [redacted] (Date)

E

This test substance is suitable for [redacted] safety testing

Originator's Sig[redacted] (signature) (Date)

Toxicologist: [redacted] (signature) 3-3-11 (Date)

HAZLETON
LABORATORIES EUROPE LTD

[redacted]

13 WEEK ORAL (DIETARY) TOXICITY STUDY IN THE RAT

[redacted], E1095.01

PEG-2 Tallow amine

Report for: [redacted]

Prepared by:

Hazleton Laboratories Europe Ltd.,
Otley Road,
Harrogate, HG3 1PY,
ENGLAND.

Report No: 2913-110/369

Date: February 1982

AUTHENTICATION **REPORT NO. 2913-110/369**

I, the undersigned, hereby declare that the work described in this report was performed under my supervision, as Study Director, in accordance with the agreed protocol, and with the Hazleton Manual of Standard Operating Procedures, unless otherwise stated, and that the report provides a true and accurate record of the results obtained.

D. B. Sheppard, B.Sc.,
Toxicologist

QUALITY ASSURANCE RECORD **REPORT NO. 2913-110/369**

The project described in this report was subject to audit/inspection by the independent HLE Quality Assurance Unit for the aspects and at the intervals specified below. The findings of each audit, unless indicated otherwise, were reported to HLE management and to the Study Director as prescribed by Standard Operating Procedures.

Phase of study audited	Audit date
Study inspection	September 1981
Study inspection	October 1981
Study inspection	November 1981
Final report	April 1982

Pamela R. Cooper

Pamela R. Cooper, B.Sc., Ph.D., M.P.S.
Quality Assurance Manager

Date: 28 February 1983

CONTENTS

CONTENTS (continued)

CONTENTS (continued)

HLE Project no. 110/369

SECTION A

1. SUMMARY

1.1 Three groups of rats, each comprising 20 males and 20 females, were fed diets containing E1095.01 at concentrations of 0.001, 0.015 and 0.5% w/w. A similar group of rats fed untreated diets acted as a control group.

1.2 All rats survived the 13 week treatment period except for one control female rat which died during the blood sampling procedure in week 13.

1.3 There was a high incidence of hairloss. As the number of rats affected was similar in the controls and the treated groups this is considered not to be treatment-related.

1.4 Body weight gain was slightly reduced in the group 4 males and females and in the group 3 males.

1.5 Food consumption in the groups of treated rats was comparable with that of the control group during the study. Food conversion efficiencies were generally comparable in all groups throughout the study.

1.6 There were no biologically significant differences in haematology between the treated and control groups during week 13.

1.7 There were no changes in organ weights that could be attributed to administration of the test article.

1.8 The only treatment-related histopathological finding was histiocytosis in group 4. The histiocytosis was characterised by foamy macrophage aggregation in the jejunum and mesenteric lymph nodes. Examination of these tissues in group 2 and 3 rats revealed no histiocytosis.

1.9 In conclusion, the highest "no effect" dose level in this study was 0.015% w/w E1095.01 in the diet.

2. INTRODUCTION

The purpose of this study was to investigate the potential systemic toxicity of E1095.01 administered for 13 weeks by admixture in the diet.

The rat was chosen as the experimental model since it is a commonly used rodent species with documented susceptibility to a wide range of substances.

Administration of the test diets started on 28 July 1981 and the animals were killed on 27-30 October 1981.

3. EXPERIMENTAL PROCEDURES

3.1 Protocol adherence

The first dose range-finding study (110/368) was conducted in accordance with Protocol number P1393/21/4/3/552/d (Appendix 1) but the associated 13 week study was abandoned. The new 13 week study (110/369) and second dose range-finding study (110/376) were conducted in accordance with Protocol number P1416/d and authorised amendments (presented as Appendix 10) but with the following exceptions:

Section 2.7

50g samples of the diet formulations were retained and not 100g samples.

Section 3.3

The animals were approximately 6½ weeks of age instead of 5 weeks as specified in protocol.

Section 3.4

On one occasion the temperature fell to 18°C and the relative humidity exceeded the specified maximum on 2 occasions by 2% and on another 2 occasions by 5%.

These deviations were considered not to have affected the integrity or outcome of the study.

3.2 Test and control article

3.2.1 Description, identification and storage

The test article, a yellow viscous liquid, was identified as E1095.01; Hazleton Dispensary number 1/82-110 and was supplied by the study sponsor. No batch number was provided for the test article used in this study. The test article was stored at room temperature with the container lids tightly closed.

3.2.2 Route and method of administration

The test article was administered orally by admixture with the diet. This route of exposure was chosen by the sponsor since accidental ingestion is a potential route of human exposure.

3.2.3 Dietary concentration

The dietary concentrations used in this study were 0.001, 0.015 and 0.5% w/w. These concentrations were chosen after consideration of data from the second of two 2 week dose range-finding studies (HLE project number 110/376) in the rat, performed at HLE (Appendices 8 and 9).

Control animals were fed untreated powdered diet.

3.2.4 Frequency and duration of administration

The test or control diet mixes were fed continuously for 13 weeks. In addition, as there were more animals for necropsy at 13 weeks than could be handled on a single day, there was an across group staggered necropsy schedule. Animals were fed the experimental diets until necropsy.

3.2.5 Frequency of preparation

Separate batches of diet were prepared for each treatment group at weekly intervals throughout the study.

Surplus diets were discarded after 7 days' use.

3.2.6 Method of diet preparation

Batches of each diet mix (10 kg) were prepared at weekly intervals on a constant % w/w basis throughout the study as follows:

1% corn oil (Boots Pure Drug Co. Ltd., Nottingham) was added to the preweighed amount of the test article for the particular group. This mixture was stirred mechanically until homogenous and then added to a small amount of diet in a mortar. This mixture was triturated until homogeneous and then mixed on a small Hobart mixer for 2-3 minutes. More diet was then added until the weight was about 1 kg and this mixture was again mixed for about 1 minute after which it was emptied into the bulk diet and the Hobart bowl rinsed out with more diet. The bulk diet was then mixed for 10 minutes.

Sometimes, however, on addition of the test article/corn oil suspension to the small amount of diet, the suspension was destroyed producing a cake of test article-diet. When this occurred the cake was premixed further by careful addition of new lots of diet until it had been broken up and the rest of the preparation was then carried out.

Diet preparation for group 1 was as above except that no test article was included in the mixture.

Each batch of test or control diet prepared was divided into 2 equal portions for separate feeding to males and females.

The diets were held in colour coded plastic bins at room temperature. The diet bins were labelled with the test article identity, concentration, date of preparation and HLE project number.

3.2.7 Analysis of diet preparations

During the course of the study, 100 g samples of each batch of diet prepared and each batch of control diet were retained in hermetically sealed plastic bags and stored in the dark at approximately +4°C.

The accumulated samples of diet and a 20 g sample of the bulk test article were returned to the study sponsor during weeks 1, 5, 9 and 14.

3.2.8 Determination of degree of absorption of the test article

Determination of the degree of absorption of the test article by the test system was not requested by the study sponsor.

3.2.9 Stability of test article-diet preparation

Determination of the stability of the test article in the powdered diet was not requested by the study sponsor.

3.3 Test system

3.3.1 Species, strain and supplier

A sufficient number of Crl: CD(SD)BR rats to provide 80 healthy animals of each sex was obtained from Charles River (UK) Ltd., Manston Road, - Margate, Kent.

3.3.2 Justification for the selection of test system

There is ample evidence in the scientific literature to demonstrate the susceptibility of the rat to the toxic actions of a diverse range of substances. In addition, substantial background data for the CD strain has been documented. Therefore, in the absence of any data which preclude the use of the rat, the CD strain rat was considered suitable for this study.

3.3.3 Specification

On receipt all animals were weighed and examined for external signs of ill-health. Unhealthy animals were discarded. The animals were acclimatised for 19 days, towards the end of which the animals were reweighed and re-examined to confirm their suitability for experimental purposes.

At the start of treatment the animals were approximately 6½ weeks of age and weighed between 136-188 g for males and 119-165 g for females.

Eighty animals of each sex which showed the greatest weight gain during the acclimatisation period were selected for the study.

3.3.4 Environment

The animals were caged in groups of 5, by sex, in stainless steel mesh cages, in one room exclusive to the study. The cages were suspended over cardboard lined trays. The liners were replaced as often as was

necessary to maintain the animals in a sanitary condition. In most instances this was twice per week.

The experimental room was air-conditioned by means of a ducted ventilation system. The temperature and relative humidity of the room were normally within the ranges 18-24°C and 45-75%.

Artificial lighting (fluorescent) was automatically controlled to give a cycle of 12 hours light (0600-1800 hours) and 12 hours darkness.

3.3.5 Diet and drinking water

With the exception of an overnight period without food before necropsy, all animals had free access to food dispensed from non-spill hoppers. The diet was Rat and Mouse No. 1 SQC Modified Diet, Expanded and Reground, supplied by Special Diets Services Ltd., Stepfield, Witham, Essex which is routinely analysed by the manufacturer for some nutritional components and some specified contaminants (heavy metals, aflatoxins and insecticides). Representative analyses are presented in Appendix 2 of the protocol.

Mains water dispensed from glass bottles was freely available throughout the study. Clean water bottles were provided weekly. The water is periodically analysed for heavy metals and chlorinated hydrocarbons by the local water authority. In addition, periodic analyses of the levels of polycyclic aromatic hydrocarbons is carried out by HLE. Representative analyses are presented in Appendix 3 of the protocol.

Constituents of the diet or water reasonably expected to interfere with the objective of this study have been considered by the sponsor and by HLE. No contaminants are thought to be present in the diet or water at levels which might prevent the achievement of the study objectives.

3.3.6 Randomisation

The animals were randomised into treatment groups using a stratified body weight technique to produce similar group mean body weights at the start of treatment.

The position of the cages in the battery were determined by random design.

3.3.7 Experimental design

Group number	Dietary concentration % w/w	Group description	Number of animals M	F
1	0	Control	20	20
2	0.001	Low	20	20
3	0.015	Intermediate	20	20
4	0.5	High	20	20

3.3.8 Identification of the test system

Following allocation to treatment groups each animal was assigned an individual number, permanently tattooed on the ear, according to the following schedule:

Group number	Colour code	Animal numbers M	F
1	Buff	1-20	81-100
2	Green	21-40	101-120
3	Blue	41-60	121-140
4	Pink	61-80	141-160

Each cage of animals was identified with a group-related coloured card bearing the following information: cage number, animal numbers, sex, HLE project number, test article, dose level.

A label was also attached to the door of the study room showing room number, HLE project number, route of administration, date of commencement and Home Office licensee.

3.4 Evaluation of effects

3.4.1 Morbidity and mortality

At the beginning and end of each working day all animals were examined to detect any which were dead or moribund.

3.4.2 Clinical observations

All animals were examined at least once daily throughout the study for signs of ill-health, overt toxicity or behavioural change. An individual record of clinical changes observed was maintained for each animal.

3.4.3 Body weight

Individual body weights were recorded prior to treatment on the first day of the study, at weekly intervals throughout the study and at necropsy.

3.4.4 Food consumption

The food consumption of each cage of animals was recorded weekly throughout the study.

3.5 Laboratory methods (see Appendix 7)

Haematology analyses were performed on individual blood samples withdrawn from all animals (nonfasted) during the 13th week of treatment except for animal number 87F which died during the bleed. Blood samples, obtained by orbital sinus puncture under light anaesthesia (Diethyl ether, Analar grade, BDH Ltd., Poole, Dorset) were taken into EDTA anticoagulant tubes.

The following parameters were examined:

haemoglobin (Hb)
mean cell volume (MCV)
red blood cell count (RBC) and derived indices:
- packed cell volume (PCV)
- mean cell haemoglobin (MCH)
- mean cell haemoglobin concentration (MCHC)

total white blood cell count (WBC) and
differential white blood cell counts

3.6 Pathology

The following procedure was adopted at the end of the study.

3.6.1 Necropsy

All animals surviving the 13 week treatment period were killed by an intraperitoneal injection of pentobarbitone sodium solution (Euthatal, 200 mg/ml, May & Baker, Dagenham, Essex) following an overnight fast of approximately 16 hours. The animals were exsanguinated immediately to standardise organ weights.

All animals, including animal number 87F, which died during the bleed, were subjected to a full internal and external postmortem examination,

including all orifices, and a full macroscopic examination of all tissues and organs was also performed.

The animals were killed in random order over 4 working days.

3.6.2 Organ weights

The following organs, dissected free from fat and other contiguous tissue, were weighed before fixation:

adrenals	heart
kidneys	liver
lungs	ovaries
testes	

Left and right organs were weighed separately where appropriate.

3.6.3 Histopathology

Samples of the following tissues and organs (with the exception of the bone marrow smear which was fixed in methanol and the eyes which were fixed in Davidson's fluid) were fixed in 10% neutral buffered formalin:

adrenals	aorta
bladder	bone marrow smear
brain	caecum
colon	duodenum
epididymides	eyes
gross lesions	heart
ileum	jejunum
kidneys	liver
lungs	mandibular salivary gland and lymph node
mesenteric lymph node	ovary/testis
oesophagus	pituitary
pancreas	sciatic nerve
psoas muscle	skin
seminal vesicle	stomach
spleen	thyroids
thymus (where present)	trachea
tongue	
uterus/prostate	

All tissues from all animals in groups 1 and 4 and sections of jejunum and mesenteric lymph nodes from groups 2 and 3 were prepared as paraffin blocks (mp 56°C), sectioned at a nominal thickness of 5 µm and stained with haematoxylin and eosin. The remaining tissues from groups 2 and 3 were retained in fixative only.

All stained sections were examined by light microscopy by the study director under the supervision of a qualified pathologist.

4. RESULTS

4.1 Survival

All rats survived the 13 week treatment period except for 87F. This rat died during the blood sampling procedure during week 13.

4.2 Clinical condition (Appendix 2)

The only notable clinical observation was a high incidence of hairloss. The incidence was approximately similar across all groups within each sex. However there was a slightly greater incidence in the males, of which approximately 70-90% were affected, than in the females, where approximately 35-70% of the rats were affected. This is considered not to be related to treatment.

4.3 Body weight (Figure 1, Table 1, Appendix 1)

Body weight gain was slightly reduced in the group 4 males, when compared to the controls, from week 3 until termination. Also, there was a slight reduction in the rate of weight gain of the group 3 male rats from week 9 of the study. This resulted in slightly reduced group mean body weights at the end of the study for groups 3 and 4, relative to the control male group.

In the female groups, rats in group 4 gained weight at a lower rate than the controls from week 5 until termination. Rats in groups 2 and 3 gained weight at a rate slightly greater than that of the controls.

4.4 Food consumption (Table 2)

There were no remarkable differences in group mean food consumption between control and treated rats throughout the study.

4.5 Food conversion efficiency (Table 3)

Food conversion efficiencies were generally comparable in all groups throughout the study.

4.6 Compound consumption (Table 4)

There was a rapid reduction in test article intake in all treatment groups during the first 3 weeks of the study. This corresponded with the period of most rapid growth of the rats. During the last 10 weeks of the study the dose levels received (in mg/kg/day) ranged between

group 2M	0.5 - 0.9	group 2F	0.8 - 1.0
group 3M	8.4 - 12.9	group 3F	11.7 - 16.1
group 4M	277 - 424	group 4F	398 - 540

4.7 Haematology (Table 5, Appendix 3)

Group mean male values for haemoglobin, red blood cell counts, packed cell volume and total white blood cell counts were increased in groups 3 and 4 compared to group 1 (controls). In the female treated groups there was a tendency for the values to be lower than in the female controls.

4.8 Organ weights (Appendix 4)

There were no remarkable differences in absolute or relative organ weights between the treated groups and the controls.

4.9 Pathology (Appendix 5)

Pathology findings in group 1 rats were generally minor and consisted of such changes as peribronchial lymphoid hyperplasia in the lungs, leucocyte foci in the liver and lymphoid hyperplasia in the small and large intestine.

Minor lesions similar to those in group 1 were seen in group 4 but additional treatment-related histiocytosis was seen in the jejunum and mesenteric lymph nodes. The histiocytosis was characterised by aggregations of histiocytes (macrophages) with foamy cytoplasm in the lamina propria of the jejunum and the sinuses of the mesenteric lymph nodes. The severity of the histiocytosis was minimal to slight and the males were slightly more affected than the females.

There was no evidence of histiocytosis in the jejunum and mesenteric lymph nodes of rats in groups 2 and 3.

5. DISCUSSION

Administration of E1095.01 in the diet at a constant concentration of 0.5% w/w produced a slight reduction in body weight gain in males and females. However, food consumption was unaffected by the incorporation of the test article. The test article also produced changes at its site of absorption (jejunum) and in the associated reticuloendothelial system - the mesenteric lymph nodes. The histological changes seen in these organs reflect uptake of dietary lipid material (test article) by histiocytes giving rise to the foamy appearance of their cytoplasm. These were not present in sections of jejunum and mesenteric lymph node from rats in groups 2 and 3.

There was no evidence of systemic toxicity in groups 2 and 3 so the highest "no effect" level in this study was 0.015% w/w E1095.01.

6. ARCHIVE

All primary data or copies thereof, and specimens will be retained in the HLE archive 2 years after submission of the final report. At this time we will discuss with the sponsors whether or not they require storage for a longer period, either at HLE for which an archiving charge will be made or in the sponsors' own archive.

Specimens will be taken to include test/control articles, any tissue, tissue blocks or slides derived from a test system for examination or analysis. Biofluids are specifically excluded from the above definition because of the lability of the constituents.

Primary data will be taken to include laboratory data sheets, records, memoranda, notes, photographs, microfilm and computer records that are a result of the original observations and activities of the study and which are necessary for the reconstruction and evaluation of the report of the study.

SECTION B

7. TABLES

8. FIGURE

TABLE 1

Mean body weight (g), standard deviation (S.D.) and survival rate

Date of printing: 30 October 1981 Computer id. : CS1100369

Week of Study		Group and sex 1M	2M	3M	4M
Start	Mean	163.5	162.3	163.9	165.7
	S.D.	11.64	13.12	10.67	11.20
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
1	Mean	217.5	217.9	218.9	214.7
	S.D.	13.16	16.13	14.61	14.42
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
2	Mean	256.9	264.1	265.3	259.7
	S.D.	21.37	18.92	17.79	16.34
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
3	Mean	303.5	304.5	303.6	295.7
	S.D.	22.26	24.12	23.24	19.69
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
4	Mean	336.8	340.5	338.9	323.8
	S.D.	26.97	27.13	28.21	22.43
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
5	Mean	368.1	368.8	364.5	352.4
	S.D.	31.59	29.73	34.33	25.28
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
6	Mean	393.7	392.7	390.4	377.0
	S.D.	33.90	31.92	38.14	28.27
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
7	Mean	414.9	412.7	410.1	395.6
	S.D.	35.68	34.80	39.26	29.52
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
8	Mean	433.7	432.7	426.8	407.7
	S.D.	37.07	34.70	42.57	33.10
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
9	Mean	449.5	447.7	438.8	421.5
	S.D.	40.59	36.04	42.82	34.74
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
10	Mean	466.1	463.2	452.2	438.0
	S.D.	42.38	37.05	46.96	35.74
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20

TABLE 1 (continued)

Week of Study		Group and sex 1M	2M	3M	4M
11	Mean	476.6	473.2	458.3	443.7
	S.D.	42.71	39.09	49.46	38.17
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
12	Mean	488.1	483.7	468.1	452.3
	S.D.	47.49	39.38	50.53	38.56
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
13	Mean	490.3	487.0	474.6	456.6
	S.D.	48.09	39.29	56.78	40.56
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20

TABLE 1 (continued)

Mean body weight (g), standard deviation (S.D.) and survival rate

Date of printing: 30 October 1981 Computer id. : CS1100369

Week of Study		Group and sex 1F	2F	3F	4F
Start	Mean	137.8	139.9	138.9	137.9
	S.D.	8.67	10.59	9.30	9.28
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
1	Mean	164.8	165.1	167.6	162.3
	S.D.	9.53	10.88	10.89	9.10
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
2	Mean	183.4	184.7	187.0	180.3
	S.D.	9.77	13.54	15.62	11.71
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
3	Mean	199.7	199.3	202.1	195.7
	S.D.	10.74	13.06	17.12	12.74
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
4	Mean	209.3	213.5	215.3	205.0
	S.D.	12.60	15.47	18.56	13.41
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
5	Mean	222.8	221.9	229.0	217.0
	S.D.	17.36	17.23	20.25	15.65
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
6	Mean	231.1	233.8	239.1	229.2
	S.D.	14.60	17.03	22.09	14.59
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
7	Mean	237.5	242.3	244.4	232.6
	S.D.	14.81	17.95	23.44	14.55
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
8	Mean	242.5	249.9	251.9	235.3
	S.D.	14.52	18.62	24.47	15.86
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
9	Mean	248.3	250.8	257.8	239.1
	S.D.	15.09	26.68	24.99	13.43
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
10	Mean	254.6	259.3	266.2	247.2
	S.D.	16.75	21.40	25.78	16.12
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20

TABLE 1 (continued)

Week of Study		Group and sex 1F	2F	3F	4F
11	Mean	257.8	269.9	269.4	250.9
	S.D.	17.04	19.02	26.64	16.55
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
12	Mean	263.1	271.1	272.8	251.8
	S.D.	18.98	21.52	27.08	18.12
	Adjusted survival	20/ 20	20/ 20	20/ 20	20/ 20
13	Mean	265.7	272.6	276.0	251.4
	S.D.	21.67	26.23	32.19	20.30
	Adjusted survival	19/ 19	20/ 20	20/ 20	20/ 20

TABLE 2

Mean food consumption (g/week), and standard deviation (S.D.)

Date of printing: 30 October 1981 Computer id. : C31100369

Week of Study		Group and sex 1M	2M	3M	4M
1	Mean	183.6	182.5	183.5	174.2
	S.D.	5.93	6.30	4.56	4.18
2	Mean	182.8	187.8	186.5	181.3
	S.D.	4.87	8.31	4.75	5.13
3	Mean	194.3	198.5	195.3	191.6
	S.D.	15.63	9.21	6.85	9.09
4	Mean	189.4	201.1	193.3	184.0
	S.D.	12.68	22.85	7.80	9.65
5	Mean	188.7	194.4	188.3	186.3
	S.D.	13.30	7.62	4.63	3.24
6	Mean	195.4	203.6	191.6	187.7
	S.D.	6.59	24.66	5.68	3.35
7	Mean	194.3	191.6	192.9	185.0
	S.D.	5.08	12.23	9.14	5.88
8	Mean	199.0	195.0	193.7	186.8
	S.D.	7.23	7.49	5.55	5.73
9	Mean	192.0	196.9	190.9	188.3
	S.D.	6.25	8.66	6.92	5.50
10	Mean	190.3	188.1	183.9	177.2
	S.D.	8.61	5.54	11.92	3.53
11	Mean	198.1	194.4	185.8	185.2
	S.D.	4.11	7.62	12.38	7.14
12	Mean	181.3	184.4	173.4	173.5
	S.D.	6.07	10.44	12.76	14.44
13	Mean	182.5	186.9	184.3	175.9
	S.D.	16.00	11.84	22.52	7.33

TABLE 2 (continued)

Mean food consumption (g/week), and standard deviation (S.D.)

Date of printing: 30 October 1981 Computer id. : C91100369

Week of Study		Group and sex 1F	2F	3F	4F
1	Mean	137.2	139.3	141.0	142.7
	S.D.	8.18	4.66	5.99	6.51
2	Mean	138.9	144.9	144.2	149.8
	S.D.	6.95	5.17	6.34	5.69
3	Mean	168.5	155.9	157.0	158.9
	S.D.	11.68	9.29	9.60	8.33
4	Mean	150.7	151.2	156.6	151.4
	S.D.	9.52	6.24	5.59	6.59
5	Mean	148.2	158.1	151.8	152.4
	S.D.	9.01	4.85	6.78	4.92
6	Mean	153.2	152.0	150.5	151.3
	S.D.	7.91	5.85	5.86	7.37
7	Mean	150.1	151.0	150.2	151.6
	S.D.	10.38	5.58	3.57	7.73
8	Mean	163.4	157.5	157.1	158.4
	S.D.	8.02	4.83	6.72	4.14
9	Mean	156.0	167.3	164.2	154.9
	S.D.	1.30	18.09	8.36	4.01
10	Mean	149.2	158.3	165.0	148.4
	S.D.	4.18	5.17	23.29	4.91
11	Mean	156.4	159.4	163.0	146.4
	S.D.	6.83	6.96	3.09	3.55
12	Mean	151.3	156.0	145.9	138.6
	S.D.	15.28	10.38	4.62	6.31
13	Mean	147.4	156.9	149.4	140.2
	S.D.	15.10	14.47	11.49	7.71

TABLE 3

Mean food conversion efficiency (percent)
and standard deviation (S.D.)

Date of printing: 30 October 1981 Computer id. : CS1100369

Week of Study		Group and sex 1M	2M	3M	4M
1	Mean	29.4	30.5	30.0	28.1
	S.D.	.00	.00	.00	.00
2	Mean	21.5	24.6	24.9	24.8
	S.D.	.00	.00	.00	.00
3	Mean	24.0	20.4	19.6	18.8
	S.D.	.00	.00	.00	.00
4	Mean	17.6	17.9	18.3	15.3
	S.D.	.00	.00	.00	.00
5	Mean	16.6	14.6	13.6	15.4
	S.D.	.00	.00	.00	.00
6	Mean	13.1	11.7	13.5	13.1
	S.D.	.00	.00	.00	.00
7	Mean	10.9	10.4	10.2	10.0
	S.D.	.00	.00	.00	.00
8	Mean	9.5	10.3	8.6	6.5
	S.D.	.00	.00	.00	.00
9	Mean	8.2	7.6	6.3	7.3
	S.D.	.00	.00	.00	.00
10	Mean	8.7	8.3	7.3	9.3
	S.D.	.00	.00	.00	.00
11	Mean	5.3	5.1	3.3	3.1
	S.D.	.00	.00	.00	.00
12	Mean	6.3	5.7	5.6	5.0
	S.D.	.00	.00	.00	.00
13	Mean	1.2	1.8	3.6	2.5
	S.D.	.00	.00	.00	.00

TABLE 3 (continued)

Mean food conversion efficiency (percent)
and standard deviation (S.D.)

Date of printing: 30 October 1981 Computer id. : CS1100369

Week of Study		Group and sex 1F	2F	3F	4F
1	Mean	19.7	18.1	20.3	17.2
	S.D.	.00	.00	.00	.00
2	Mean	13.4	13.5	13.5	12.0
	S.D.	.00	.00	.00	.00
3	Mean	9.6	9.4	9.6	9.7
	S.D.	.00	.00	.00	.00
4	Mean	6.4	9.4	8.4	6.2
	S.D.	.00	.00	.00	.00
5	Mean	9.1	5.3	9.0	7.8
	S.D.	.00	.00	.00	.00
6	Mean	5.4	7.9	6.7	8.0
	S.D.	.00	.00	.00	.00
7	Mean	4.2	5.6	3.6	2.3
	S.D.	.00	.00	.00	.00
8	Mean	3.1	4.9	4.8	1.7
	S.D.	.00	.00	.00	.00
9	Mean	3.7	.5	3.6	2.4
	S.D.	.00	.00	.00	.00
10	Mean	4.2	5.4	5.1	5.5
	S.D.	.00	.00	.00	.00
11	Mean	2.1	6.7	2.0	2.5
	S.D.	.00	.00	.00	.00
12	Mean	3.5	.8	2.4	.7
	S.D.	.00	.00	.00	.00
13	Mean	1.9	.9	2.1	-.3
	S.D.	.00	.00	.00	.00

TABLE 4

Compound consumption (mg/kg/day)

Date of printing: 30 October 1981 Computer id. : CS1100369

Week of Study		Group and sex 1M	2M	3M	4M
Start	Mean	.0	.0	.0	.0
	Corrected	.0	.0	.0	.0
1	Mean	.0	1.4	20.5	654.2
	Corrected	.0	1.4	20.5	654.2
2	Mean	.0	1.1	16.5	546.0
	Corrected	.0	1.1	16.5	546.0
3	Mean	.0	1.0	14.7	492.8
	Corrected	.0	1.0	14.7	492.8
4	Mean	.0	.9	12.9	424.3
	Corrected	.0	.9	12.9	424.3
5	Mean	.0	.8	11.5	393.6
	Corrected	.0	.8	11.5	393.6
6	Mean	.0	.8	10.9	367.6
	Corrected	.0	.8	10.9	367.6
7	Mean	.0	.7	10.3	342.0
	Corrected	.0	.7	10.3	342.0
8	Mean	.0	.7	9.9	332.3
	Corrected	.0	.7	9.9	332.3
9	Mean	.0	.6	9.5	324.4
	Corrected	.0	.6	9.5	324.4
10	Mean	.0	.6	8.8	294.6
	Corrected	.0	.6	8.8	294.6
11	Mean	.0	.6	8.7	300.0
	Corrected	.0	.6	8.7	300.0
12	Mean	.0	.6	8.0	276.7
	Corrected	.0	.6	8.0	276.7
13	Mean	.0	.5	8.4	276.5
	Corrected	.0	.5	8.4	276.5

TABLE 4 (continued)

Compound consumption (mg/kg/day)

Date of printing: 30 October 1981 Computer id. : CS1100369

Week of Study		Group and sex 1F	2F	3F	4F
Start	Mean	.0	.0	.0	.0
	Corrected	.0	.0	.0	.0
1	Mean	.0	1.3	19.7	679.0
	Corrected	.0	1.3	19.7	679.0
2	Mean	.0	1.2	17.4	624.7
	Corrected	.0	1.2	17.4	624.7
3	Mean	.0	1.2	17.3	603.6
	Corrected	.0	1.2	17.3	603.6
4	Mean	.0	1.0	16.1	539.6
	Corrected	.0	1.0	16.1	539.6
5	Mean	.0	1.0	14.6	516.0
	Corrected	.0	1.0	14.6	516.0
6	Mean	.0	1.0	13.8	484.5
	Corrected	.0	1.0	13.8	484.5
7	Mean	.0	.9	13.3	469.1
	Corrected	.0	.9	13.3	469.1
8	Mean	.0	.9	13.6	483.7
	Corrected	.0	.9	13.6	483.7
9	Mean	.0	1.0	13.8	466.4
	Corrected	.0	1.0	13.8	466.4
10	Mean	.0	.9	13.5	436.0
	Corrected	.0	.9	13.5	436.0
11	Mean	.0	.9	13.0	419.9
	Corrected	.0	.9	13.0	419.9
12	Mean	.0	.8	11.5	393.9
	Corrected	.0	.8	11.5	393.9
13	Mean	.0	.8	11.7	398.0
	Corrected	.0	.8	11.7	398.0

TABLE 5

Group mean haematology data

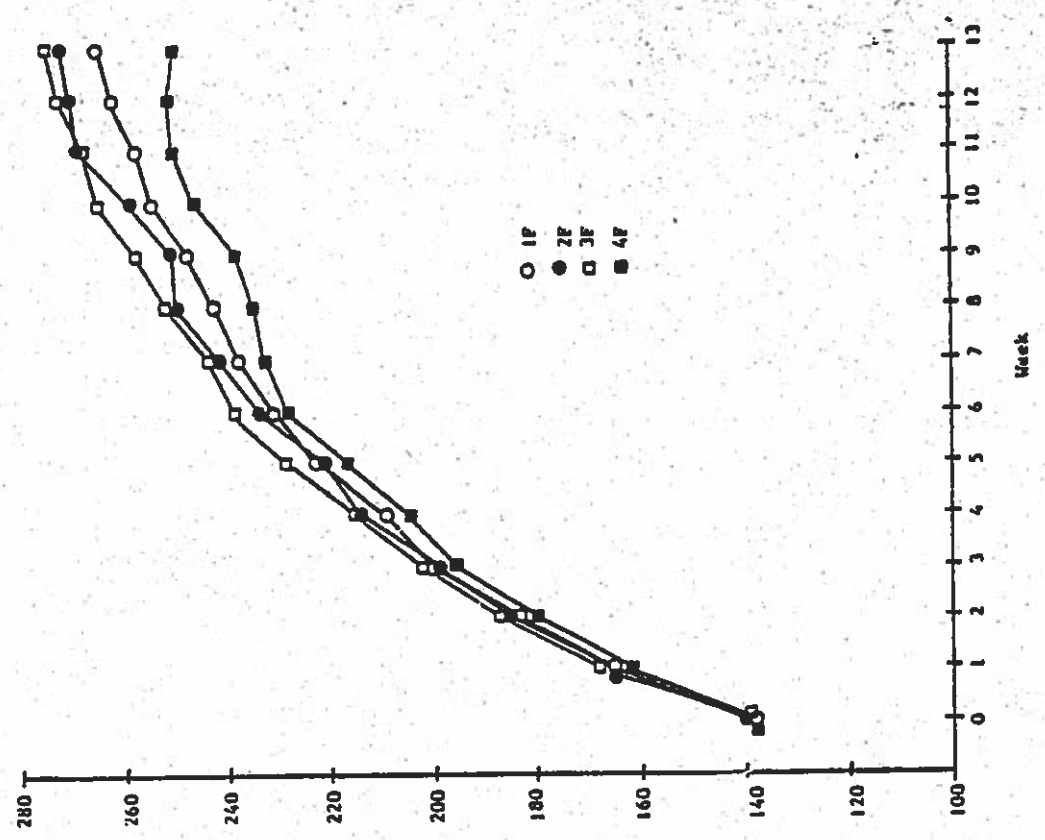
WEEK 13

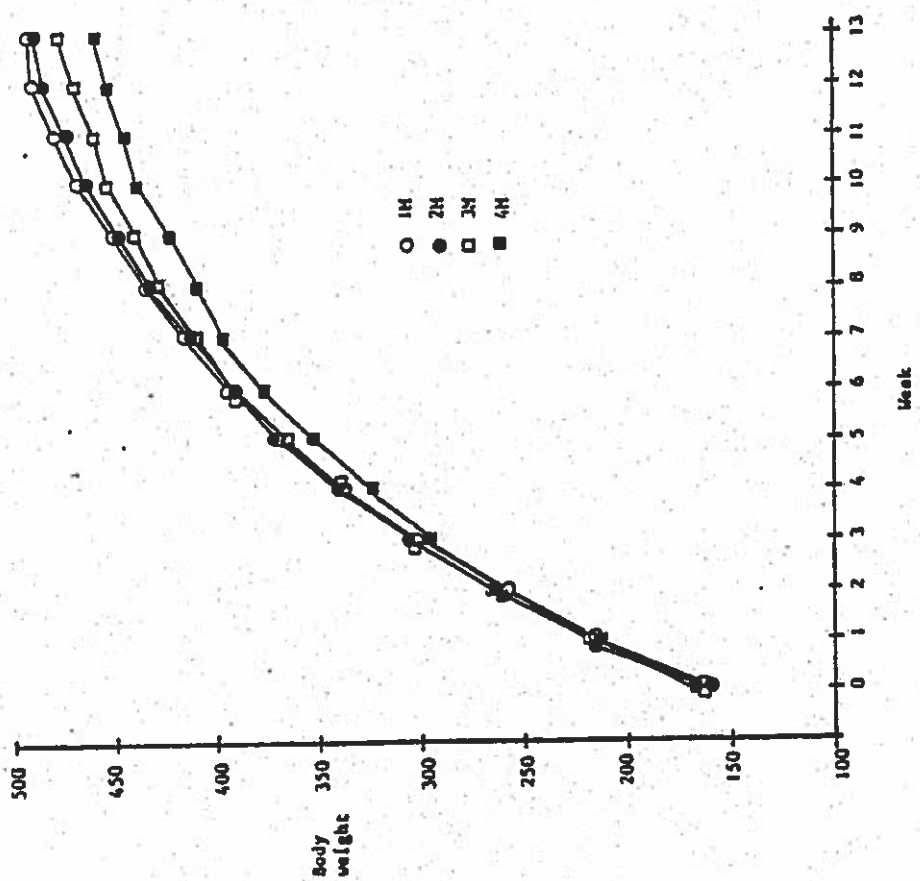
Group number/ sex	Hb g/dl	RBC mil. /cmm.	PCV %	MCH pg	MCHC g/dl	MCV cμm	WBC 1000/cmm Total	N	L	M	E	B
1M	16.1(.5)	8.15(.45)	44(2)	19.8(1.0)	37(1)	55(2)	17.79(3.09)	2.51(1.28)	15.19(2.15)	.07(.13)	.02(.07)	.00(.00)
2M	16.0(.3)	8.14(.30)	44(1)	19.7(.8)	37(1)	54(2)	17.60(2.83)	2.24(.90)	15.30(2.60)	.05(.09)	.01(.05)	.00(.00)
3M	16.6(.5)	8.69(.34)	48(1)	19.2(.7)	35(1)	54(2)	18.90(3.48)	2.28(.87)	16.59(3.01)	.02(.06)	.01(.03)	.00(.00)
4M	16.5(.5)	8.85(.39)	47(1)	18.7(.5)	35(1)	53(2)	21.05(3.79)	2.20(.77)	18.76(3.53)	.09(.14)	.01(.04)	.00(.00)
1F	16.0(.4)	8.01(.37)	45(1)	20.0(.8)	35(1)	56(2)	13.26(2.21)	1.65(.71)	11.59(1.94)	.03(.06)	.00(.00)	.00(.00)
2F	15.7(.4)	7.86(.31)	45(2)	20.0(.8)	35(1)	56(2)	12.36(2.27)	1.81(.62)	10.47(2.10)	.04(.06)	.03(.07)	.00(.00)
3F	15.7(.3)	7.76(.33)	44(1)	20.3(.7)	36(1)	56(1)	12.40(2.21)	1.65(.65)	10.69(1.86)	.05(.07)	.01(.04)	.00(.00)
4F	15.4(.5)	7.92(.34)	44(1)	19.5(.7)	35(1)	55(1)	12.20(3.17)	1.27(.43)	10.91(3.05)	.01(.03)	.01(.03)	.00(.00)

() = standard deviation

FIGURE 1

Group mean body weights (g)





Test Substance Identification Number E- 1095.01 [redacted]

[redacted]

Principal Investigator [redacted]
(Name)

Name of Product or Ingredient (or code designation) "TAMET"/BENZOATE SOLUTION

Brand Notebook Ref. (including Production Code if available) [redacted]

Physical Form LIQUID Colour PALE BROWN/YELLOW Density 1000g/l

Solubility _____ pH (conc) _____ Sample Expiration Date MARCH 1982

Recommended Storage Conditions STORE AT ROOM TEMPERATURE; 20°C

Hazards (i.e. flammability, toxic gases) _____

FORMULATED COMPOSITION

Component[a]	Nominal Level (% by Wt)	Acceptable Range[b]	Stock Code No.	Supplier	Lot Number[b] (NB-Ref)
[illegible]LLOW B-DIHYDROXYETHYL AMINE	14.9		-*	GOLDSCHMIDT	BATCH 1834
BENZOIC ACID	5.1		60064	NK	NK(SAMPLE RETAINED)
DISTILLED WATER	80		-	-	-

*STOCK CODE NO. 70308 ONLY SO FAR GIVEN FOR TAMET MATERIAL FROM AKZO CHEMIE (SUPPLIER)

(a) Ingredients will be listed by chemical name: Non-chemical names such as Tergitol 15-3-9 or Yellow Dye D&C No. 10 may be acceptable but should be previewed with the responsible toxicologist. Chemical names which are inconveniently long may be abbreviated in tables but should be listed in full in referenced footnotes. Non-definitive identifications (e.g. Arquad, BC-base) are not acceptable.

(b) If information requested is not known then the symbol NK will be entered.

The above information provided by:

DRD Originator [redacted]
(Name) (Date)

HAZLETON
LABORATORIES EUROPE LTD
Otley Road, Harrogate
North Yorkshire HG3 1PY England

- 5 JAN 1982

E1069.02 : A 4 WEEK PERCUTANEOUS TOXICITY STUDY IN THE RABBIT

[redacted] PEG-2 Tallowamine

ET BASE

Report for: [redacted]

AUTHENTICATION

I, the undersigned, hereby declare that the work described in this report was performed under my supervision, as Study Director, in accordance with the agreed protocol, and with the Hazleton Manual of Standard Operating Procedures, unless otherwise stated, and that the report provides a true and accurate record of the results obtained.

D.C. Shaw, B.Sc., Ph.D.,
Study Director

Hazleton Laboratories Europe Ltd.,
Otley Road,
Harrogate, HG3 1PY,
ENGLAND.

Report No: 2827-110/366

Date: December, 1981

ANALYTICAL REQUEST FORM

D

Please carry out the following analyses according to your recorded procedures. This data is needed for non-clinical safety studies.

Signed _____ (Name) [redacted] Date _____

Agreed for Analytical Section _____ (Name) Date _____

Agreed for Human Safety _____ (Name) Date _____

Date Submitted	Submitter Code	Component or Property	Measured Value	Analytical Notebook Ref
3-8-81	4/842D	Cat SO_3 Equiv.	2.913	
		TERTIARY Amine	2.831	
		SECONDARY Amine	0.022	
		PRIMARY Amine	0.021	1725 p.131 & 1599 p.142
		Ash	0.017	
		Volatiles	0.22	
		Nonionics	1.38	
		Lovibond RED	1.2	
		YELLOW	3.7	

GLC:- Chainlength Distribution (%)

$C_{10}E_2$ 0.3; $C_{12}E_2$ 1.6; $C_{14}E_2$ 4.4; $C_{15}E_2$ 0.5; $C_{16}E_2$ 29.9; $C_{17}E_2$ 1.5; $C_{18}E_2$ 2.3; $C_{18}E_2$ 54.4; $C_{20}E_2$ 0.9; $C_{16}E_3$ 1.2; $C_{18}E_3$ 2.0 UNKNOWN 1.0

Av. MW = 343

Analytical information verified by: [redacted] (Name) _____ (signature) 11th September 1981 (Date)

E

This test substance is suitable for non-clinical safety testing

Originator's [redacted]: _____ (Name) _____ (signature) _____ (Date)

Toxicologist: [redacted] (Name) _____ (signature) 11 September 1981 (Date)

QUALITY ASSURANCE RECORD **REPORT NO. 2827-110/366**

The project described in this report was subject to audit/inspection by the independent HLE Quality Assurance Unit for the aspects and at the intervals specified below. The findings of each audit, unless indicated otherwise, were reported to HLE management and to the Study Director as prescribed in the HLE Company Standard Procedure No. 26, "QA audit report circulation".

Phase of study audited	Audit date
In-life - 1	July/August 1981
Final report	November 1981

Pamela R. Cooper

Pamela R. Cooper, B.Sc., Ph.D., M.P.S., — 23 December 1981

Quality Assurance Manager — Date

CONTENTS

CONTENTS (continued)

CONTENTS (continued)

SECTION A

1. SUMMARY

1.1 Two groups of New Zealand White rabbits, each comprising 5 rabbits of each sex, were treated topically with aqueous dispersions of E1069.02 at concentrations of 0.1 and 0.5% w/v. The dispersions were applied at a treatment volume of 2 ml/kg to nonabraded skin for 5 consecutive days followed by 2 treatment-free days each week for 4 weeks. A further group of 5 rabbits of each sex were treated with 2 ml/kg distilled water and acted as controls.

1.2 All rabbits were examined daily for clinical changes and skin irritation was assessed. The rabbits were weighed weekly. Cellular constituents of blood were measured before the start of treatment and during the final week of the study in all rabbits. Major organs and tissues of all rabbits were examined at necropsy and a limited range weighed. Tissues from rabbits in groups 1 and 3 were examined histologically.

1.3 Repeated topical application of E1069.02 at 0.1 and 0.5% w/v elicited overt slight and moderate irritant responses, respectively.

1.4 There was no evidence of systemic toxicity from mortalities, clinical changes, haematological measurements, body and organ weights or pathological findings.

2. INTRODUCTION

The objective of this study was to assess any topical and/or systemic toxicity of the test article, E1069.02. The test article was applied topically to shaved, nonabraded skin since this is one possible route of human exposure.

The concentrations of test article used were selected from a dose ranging study (HLE report number 2759-110/365).

The experimental work described in this report was carried out during the period 9 June to 21 July 1981.

3. EXPERIMENTAL PROCEDURES

3.1 Protocol adherence

The study was carried out according to the agreed protocol (HLE Protocol number P1387/21/6/1/558/d) with the following exceptions:

3.1.1 To avoid possible ingestion of residual test article, the rabbits were placed in Elizabethan collars for 24 hours each day, 7 days/week, rather than 7 hours each day, 5 days/week. This was implemented from day 16 onwards.

3.1.2 One rabbit from group 1 (6730) was found dead after the first application, probably because of an enteric disturbance. This animal was replaced (with 6730R) and treated accordingly from day 2 onwards.

3.1.3 At the start of treatment the replacement male rabbit (6730R) and 3 female rabbits (6749, 6754, 6759) were not within the weight range 2.2 to 2.8 kg but weighed up to 3.03 kg.

The above deviations from protocol were considered not to have affected the integrity or outcome of the study.

3.2 Test and control articles

3.2.1 Description, identification and storage conditions

The test article, a pale yellow, waxy solid, was supplied by the sponsor in glass bottles labelled ECM BTS 306, E1069.02. The test article was stored as supplied at ambient temperature in the dark.

The control article and vehicle for the test article was distilled water.

3.2.2 Route and method of administration

Since one possible route of human exposure will be contact with skin, the test article was applied directly to a shaved area of skin (approximately 10 x 10 cm) on the dorso-lumbar region.

The test and control articles were applied topically using a ball-ended stainless steel cannula and plastic disposable syringes. The test article dispersions were shaken before use to ensure a uniform mix.

From day 16 onwards Elizabethan collars were placed on the rabbits for 24 hours/day, 7 days/week to minimise ingestion of test article. Before day 16 the collars were removed after 7 hours. Throughout the study seven hours after treatment the application sites were washed with warm tap water and then blotted dry.

The application sites were shaved as necessary to maintain the area free of fur.

3.2.3 Dose levels

The volume of test or control article applied to each animal was calculated on individual body weight at the start of each week.

Group number	Control/ test article	Group description	Concentration of test article % w/v
1	Distilled water	Control	N/A
2	E1069.02 in vehicle	Low	0.1
3	E1069.02 in vehicle	High	0.5

N/A Not applicable
A treatment volume of 2 ml/kg/day was used for all groups.

3.2.4 Frequency of administration

Test and control articles were applied once daily, on 5 consecutive days per week, for 4 weeks.

3.2.5 Method and frequency of test article preparation

Fresh dispersions of the test article were prepared daily by mixing with distilled water. Surplus test article preparations were discarded.

3.2.6 Proof of absorption of test article

Proof of absorption of the test article by the test system was not investigated at the request of the study sponsor.

3.2.7 Analysis of stability and concentration of test article preparations

No samples for determination of stability were retained since the test article dispersions were applied to the animals within 3 hours of preparation.

100 ml samples of each test article solution and control article (vehicle) were returned to the study sponsor at the end of weeks 1 and 4, for analysis of test article concentrations. Results of the analyses are not available from the study sponsor and are not included in this report.

3.3 Test system

3.3.1 Species/strain/supplier

A sufficient number of New Zealand White rabbits to provide 15 healthy male and 15 healthy female rabbits were obtained from Morton Commercial Rabbits, Parsonage Farm, Stanstead, Essex.

3.3.2 Justification for the selection of test system

The New Zealand White rabbit was chosen by the study sponsor as the results of percutaneous toxicity tests in rabbits relate well to human hand immersion tests.

3.3.3 Specification

On receipt, all rabbits were examined for external signs of ill-health or injury. The rabbits were acclimatised to the conditions within the experimental room for 13 days before the start of treatment. Towards the end of acclimatisation the rabbits were re-examined and their suitability for experimental purposes confirmed. One rabbit from group 1 (6730) was found dead after the first application. This animal was replaced (with 6730R) and treated accordingly from day 2 onwards. At the start of treatment, male rabbits were within the body weight range 2.23 to 2.88 kg and females within the range 2.31 to 3.03 kg.

3.3.4 Husbandry

The rabbits were housed individually in grid-floor cages in a single experimental room maintained at between 12 to 26°C. The relative humidity was in the range 55 to 76%. A constant artificial photoperiod of 14 hours light (06.00-20.00 hours) and 10 hours darkness.

3.3.5 Diet

Throughout the study the rabbits were given free access to diet.

On arrival and for the first 24 hours the animals were offered Spillers Rabbit Diet (Spillers Agriculture Ltd., Gainsborough, Lincolnshire) which is the diet used by the animal supplier. This diet was replaced by SQC Beta Standard Rabbit diet (BP Nutrition (UK) Ltd., Stepfield, Witham, Essex) within 48 hours of arrival.

The Beta rabbit diet was then used throughout the experiment.

Tap water was provided ad libitum and dispensed from automatic drinking valves.

3.4 Randomisation

The animals were randomly allocated to treatment groups by means of random permutation tables. Cage positions within the battery were also randomly allocated. Male and female rabbits were randomised separately for both group allocation and cage position.

3.5 Experimental design

Group number	Control/test articles	Group description	Number of animals	
			Male	Female
1	Distilled water	Control	5	5
2	E1069.02 in vehicle	Low	5	5
3	E1069.02 in vehicle	High	5	5

The surviving rabbits were treated for 4 weeks and then killed.

3.6 Identification of test system

After random allocation to treatment groups each rabbit was permanently identified by metal ear tag, according to the following schedule:

Group	Colour	Identification number of animals	
		Male	Female
1	Buff	6730-6734	6745-6749
2	Green	6735-6739	6750-6754
3	Pink	6740-6744	6755-6759

Each cage was labelled with a group-related coloured card bearing the following information: HLE project number, animal number, sex, HLE dispensary number, date of start of treatment and Home Office licensee.

3.7 Evaluation of effects

Observations on day 1 of treatment were made just before the first application of the test article.

3.7.1 Appearance, behaviour and general observation

All rabbits were examined at least once daily for signs of ill-health or overt toxicity. Any clinical changes were recorded on individual case history sheets.

3.7.2 Body weight

Individual body weights were recorded on the first day of test and at weekly intervals throughout the study.

3.7.3 Skin irritation

Skin irritation at the application site was assessed daily according to the following scale:

Erythema	0 - none 1 - slight (barely perceptible) 2 - moderate (well defined) 3 - severe (beet redness)
Oedema	0 - none 1 - slight (barely perceptible) 2 - moderate (raised approx. 1 mm) 3 - severe (raised by more than 1 mm)
Atonia (not including eschar area)	0 - normal 1 - slight impairment of elasticity 2 - moderate (slow return to normal 3 - marked (no elasticity)
Desquamation (not including eschar area)	0 - none 1 - slight scaling 2 - moderate (scabs and flakes) 3 - marked (pronounced flaking with denuded areas)
Fissuring	0 - none 1 - slight (definite cracks in epidermis) 2 - moderate (cracks in dermis) 3 - marked (cracks with bleeding)

Presence of eschar formation and exfoliation.

3.8 Laboratory analyses (Haematology)

Individual blood samples were collected from the marginal ear vein of all rabbits (nonfasted) during the week before the start of treatment.

Blood (1 ml) was collected into tubes containing EDTA anticoagulant and the following measured:

haemoglobin (Hb)
red blood cell count (RBC)
mean corpuscular volume (MCV)
white blood cell count (WBC)
differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils)

The following were derived:

packed cell volume (PCV)
mean corpuscular haemoglobin (MCH)
mean corpuscular haemoglobin concentration (MCHC)

The methods used are given in Appendix 8.

3.9 Pathology

The following procedure was applied to all rabbits killed at termination, those rabbits killed *in extremis* and where possible to those found dead.

3.9.1 Necropsy

The rabbits were killed by intravenous overdose of pentobarbitone sodium solution (Euthatal, 200 mg/ml, May & Baker, Dagenham, Essex). Major organs and tissues from all rabbits were examined for the presence of gross lesions.

Since the number of rabbits for necropsy was greater than could be handled on a single day, an across-group necropsy schedule was adopted. Similar numbers of male and female rabbits from each group were killed on each day. The necropsies were conducted over a 2 day period.

3.9.2 Organ weights

The adrenals, heart, liver, kidneys, lungs and ovaries or testes from all rabbits were weighed before fixation.

3.9.3 Histology

Samples of the following organs and tissues from all rabbits were fixed in 10% buffered formalin (with the exception of the bone marrow smear which was fixed in methanol):

adrenals	bone marrow	brain
caecum	colon	duodenum
heart	ileum	jejunum
kidneys	liver	lungs
lymph node (mesenteric)		lymph nodes (mandibular)
muscle (psoas)	oesophagus	
ovaries	pancreas	pituitary
prostate	salivary gland	sciatic nerves
seminal vesicles	skin (treated)	skin (untreated)
spleen	stomach	testes
thymus	thyroids/parathyroids	tongue
trachea	ureters	urethra (near bladder)
urinary bladder	uterus	
vaginal wall	gross lesions	

To obtain a representative area of skin a section about 5 cm wide and the length of the application site was taken at necropsy.

The tissues listed above with exception of bone marrow from all rabbits in groups 1 and 3 were processed through to paraffin wax blocks which were then sectioned at a nominal 5 µm and stained with haematoxylin and eosin.

3.10 Evaluation of effects

3.10.1 Evaluation of histopathology

All tissues listed in section 3.9.3 from all rabbits in groups 1 and 3 were examined microscopically by the study pathologist.

3.10.2 Statistical evaluation

Data were processed to give group mean values and standard deviations where appropriate.

4. RESULTS

4.1 Mortalities and clinical observations (Appendix 1)

Three male and 3 female rabbits died or were killed because of illness before termination of the study. Clinical signs or pathological findings suggest that death was due to respiratory, enteric or neurological disturbance. These deaths were not treatment-related.

Another male rabbit showed clinical signs of respiratory difficulty and lethargy but this again was not treatment-related.

4.2 Body weight (Appendix 2)

There was no effect of treatment on body weights.

4.3 Skin irritation (Appendix 3)

Irritation of the skin at the application site developed in all rabbits from group 3 during the 24 hours after the first treatment and persisted throughout the study. Skin irritation was characterised initially by slight erythema and also in some rabbits, slight oedema, which developed into moderate erythema in most rabbits after the second application of the test article. Slight to moderate fissuring and atonia with wrinkled skin and slight desquamation also developed during the first half of the study.

A reaction to treatment characterised by slight erythema was seen in 5 group 2 animals after 2 days of treatment, this developed into moderate erythema after 4 days of treatment in 2 animals. Slight oedema, desquamation and wrinkled skin also developed in most animals.

The presence of a thick layer of skin prevented assessment of oedema and atonia in 1 group 3 animal on days 9 and 10.

No reaction to treatment was observed in group 1 animals.

4.4 Haematology (Appendix 4)

There were no treatment-related effects on the cellular constituents of blood during the study.

4.5 Organ weights (Appendices 5 and 6)

There were no treatment-related effects on organ weights or organ/body weight ratios.

4.6 Pathology (Appendix 7)

The skin reaction found in all group 3 rabbits was assessed histologically as slight to moderate. It was characterised by slight to moderate acanthosis, hypergranulosis and hyperkeratosis accompanied by slight congestion, oedema and leucocyte infiltration in the superficial dermis. One rabbit (6757F) which died during the study had an acute inflammatory reaction in the treated skin site. Some group 1 rabbits had a few minor changes in the treated skin site.

There was no evidence of systemic toxicity. Infrequent pathological findings of a minor nature were noted in surviving rabbits from both groups 1 and 3.

5. DISCUSSION

Repeated topical application of E1069.02 at 0.1 and 0.5% w/v to the non-abraded skin of rabbits elicited overt slight and moderate irritant responses, respectively.

There was no evidence of systemic toxicity from mortalities, clinical changes, haematological measurements, body and organ weights or pathological findings.

6. ARCHIVE

All primary data and specimens will be retained in the HLE archive for 2 years after submission of the final report. At the end of this period we will discuss with the sponsors whether they require storage for a longer period, either at HLE for which an archiving charge will be made or in the sponsors' own archive.

Specimens will be taken to include test/control articles, any tissue, tissue block or slides derived from a test system for examination or analysis. Biofluids are specifically excluded from the above definition because of the lability of the constituents.

Primary data will be taken to include laboratory data sheets, records, memoranda, notes, photographs, microfilm, computer records that are a result of the original observations and activities of the study and which are necessary for the reconstruction and evaluation of the report of the study.

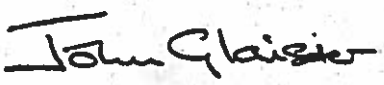
HLE Project no. 110/366

APPENDIX 7

PATHOLOGY REPORT

E1069.02: A 4 week percutaneous toxicity study in the rabbit

I, the undersigned, hereby declare that the findings described in this appendix were compiled by me or under my supervision and accurately reflect the primary data records.



J.R. Glaister, BVM & S, DVSM, Ph.D, MRCVS.
Head of Pathology

CONTENTS

HLE Project no. 110/366

1. SUMMARY

Skin irritation was assessed histologically as slight to moderate in group 3 rabbits.

There was no evidence of any systemic toxicity.

2. METHODS

2.1 Necropsy and histopathology

Necropsy procedures, tissue sampling and histology methods were as stated in the main body of the report. In summary, the major tissues and organs of all rabbits were examined at necropsy and those of rabbits in groups 1 and 3 histologically. The treated skin sites of these rabbits were scored for various responses on a semi-quantitative scale of 1-5 (minimal-severe). Tissues from group 2 rabbits were not examined histologically.

2.2 Data compilation

The necropsy data presented were derived from descriptions recorded during the postmortem examination of each animal. The data were generally presented verbatim, but may have been edited slightly by the study pathologist for clarification, consistency and accuracy, or to avoid duplication. These data accurately reflect the raw data.

The histopathology data were dictated or recorded by the study pathologist during the histological evaluation of the stained slides. These data are the verified transcription of the primary or raw data. Tissues not described were considered unremarkable by light microscopy. A full list of tissues examined histologically is presented in section 6.3.

Histological changes were described, where possible, according to their distribution, severity and morphological character. Distribution was described as focal, multifocal, diffuse, unilateral, bilateral etc., and severity scores assigned as follows:

minimal - just detectable or very mild change.

slight - fairly easily detected, but not extensive.

moderate - easily detected, e.g. up to approximately half of area or organ affected.

marked - obvious or extensive change, e.g. more than half of area or organ affected.

severe - extreme or widespread change.

The incidence of pathology findings is summarised in tabular form. The summary tabulations are intended to overview all the pathology findings and are derived mainly from histopathology data with inclusion of necropsy data where relevant. Only salient parts of the descriptive narrative were tabulated, grading and other modifying terms being omitted, and where

appropriate, similar lesions presented under more inclusive headings for more concise tabulation.

3. RESULTS

3.1 Skin reactions (Table 5.1)

A few minor changes were noted in the treated skin site of some group 1 rabbits, but most skin sites were unremarkable.

Skin reactions were found in all group 3 rabbits. There was inter-individual variation, but in general the reaction was characterised by slight to moderate acanthosis, hypergranulosis and hyperkeratosis accompanied by slight congestion, oedema and leucocyte infiltration in the superficial dermis. The main exception was 6757F which died during the study. This animal showed a more obvious acute inflammatory reaction in the treated skin site.

3.2 Other findings (Table 5.2 and individual data)

Six rabbits (6732M, 6738M, 6739M 6753F, 6754F, 6757F) died or were killed because of illness before study termination. Clinical or pathology findings suggested respiratory, enteric or neurological disturbance as the cause of the death of these animals.

Pathological findings in the surviving group 1 and 3 rabbits were generally infrequent and of a minor nature. The more common findings included pneumonitis, periportal leucocyte foci in the liver, interstitial nephritis and encephalitis. The incidence of these was not related to treatment. A variety of less frequent changes was found, but the incidence and nature of these findings showed no obvious relationship to treatment.

4. DISCUSSION

The skin reaction in group 3 rabbits was characterised by slight to moderate epidermal proliferation accompanied by a low grade inflammatory reaction in the superficial dermis. There was some inter-individual variation, but overall, the changes were assessed as evidence of slight to moderate irritation under these conditions of exposure.

The range of pathology findings in other tissues was consistent with the expected pattern of background pathology of rabbits. There were no findings of any type or incidence to suggest any systemic toxic effect.

HAZLETON
LABORATORIES EUROPE LTD

24 JUL 1986

CONFIDENTIAL

E1069.02: 7 DAY DOSE RANGE-FINDING STUDY IN THE RABBIT

[redacted]

Report for: [redacted]

AUTHENTICATION

I, the undersigned, hereby declare that the work described in this report was performed under my supervision, as Project Manager, in accordance with the agreed protocol, and with the Hazleton Manual of Standard Operating Procedures, unless otherwise stated, and that the report provides a true and accurate record of the results obtained.

D. C. Shaw, B.Sc., Ph.D.,
Toxicologist

Hazleton Laboratories Europe Ltd.,
Otley Road,
Harrogate, HG3 1PY
England.

Report No.: 2759-110/365

Date: September 1981

QUALITY ASSURANCE RECORD

REPORT NO. 2759-110/365

The project described in this report was subject to audit/inspection by the independent HLE Quality Assurance Unit for the aspects and at the intervals specified below. The findings of each audit, unless indicated otherwise, were reported to HLE management and to the Study Director as prescribed in the HLE Company Standard Procedure No. 26, "QA audit report circulation".

Phase of study audited	Audit date
Final report	August 1981

Pamela R. Cooper

Pamela R. Cooper, B.Sc., Ph.D., M.P.S.
Quality Assurance Manager

4 September 1981
Date

CONTENTS

CONTENTS (continued)

SECTION A

1. SUMMARY

1.1 Six groups of New Zealand White rabbits, each comprising one animal of each sex were treated topically with aqueous solutions of E1069.02 at concentrations of 0.5, 2, 3, 10, 30 and 90% w/v. The solutions were applied at a treatment volume of 2 ml/kg to nonabraded skin for up to 5 consecutive days followed by a 2 day treatment-free period. Two further groups of animals consisting of one animal of each sex were treated with 2 ml/kg tap water and acted as controls.

1.2 No treatment-related clinical changes were observed.

1.3 Repeated application of E1069.02 at concentrations of 0.5% w/v and above elicited an overt irritant response in the nonabraded skin of rabbits. This was characterised by moderate to marked erythema, oedema, fissuring and atonia.

1.4 The skin reaction seen at a concentration of 0.5% w/v E1069.02 would preclude the use of higher dose levels in subsequent 4 and 13 week percutaneous studies.

2. INTRODUCTION

This study was carried out to determine suitable concentrations of the test article, in terms of skin irritation, for use in subsequent 4 and 13 week percutaneous studies. The test article was applied topically to shaved, nonabraded skin since this is one possible route of human exposure. The initial dose levels were selected to give a wide range of concentrations because the only data available was a primary skin irritation score of 5.1 using undiluted material. Extra, lower dose levels were selected after the results of the original dose levels showed marked irritation.

The experimental work described in this report was carried out during the period 8 June 1981 to 19 June 1981.

3. EXPERIMENTAL PROCEDURES

3.1 Protocol adherence

The study was carried out according to the agreed protocol (HLE protocol number P1385/21/6/1/558/d) with the following exceptions:

3.1.1 Test article was not applied daily on 5 consecutive days in all cases (see Appendix 1). This was because of the severity of the skin reactions.

3.1.2 At the start of treatment the additional animals were not within the weight range 2.2-2.8 kg but weighed 2.6 to 3.5 kg.

3.1.3 The extra animals were not weighed on day 8 of the study but were weighed on day 7.

3.1.4 Group 4 was given the colour code Yellow and not Blue/2.

3.1.5 Distilled water was used on day 1 when preparing the test article dispersions and not tap water.

The above deviations from protocol were considered not to have affected the integrity or outcome of the study.

3.2 Test and control articles

3.2.1 Description, identification and storage conditions

The test article, a pale yellow, waxy solid, was supplied by the sponsor in glass bottles labelled ECM BTS 306, E1069.02. The test article was stored as supplied at ambient temperature in the dark.

The control article and vehicle for the test article was tap water.

3.2.2 Route/method of administration

Since one possible route of human exposure will be contact with skin, the test article was applied directly to a shaved and nonabraded area of skin (approximately 10 x 10 cm) on the dorso-lumbar region.

The test and control articles were applied topically using a ball-ended stainless steel cannula and plastic disposable syringes.

Animals were placed in Elizabethan collars for 7 hours each day to minimise ingestion of the test article. Seven hours after treatment the collars were removed and the application sites washed with warm tap water and then blotted dry.

The application sites were shaved as necessary to maintain the area free of fur.

3.2.3 Dose levels

The volume of test or control article applied to each animal was calculated on individual body weight at the start of the week.

Group number	Control/test articles	Treatment levels	Concentration of test article % w/v	Treatment volume (ml/kg/day)
1	Tap water	control	N/A	2
2	E1069.02 in vehicle	low	3	2
3	E1069.02 in vehicle	intermediate-I	10	2
4	E1069.02 in vehicle	intermediate-II	30	2
5	E1069.02 in vehicle	high	90*	2
6	Tap water	control-II	N/A	2
7	E1069.02 in vehicle	low-II	0.5	2
8	E1069.02 in vehicle	high-II	2	2

N/A Not applicable. * Day 1 only, 80% w/v day 2 only

3.2.4 Frequency of administration

Test and control articles were applied once daily for up to 5 consecutive days followed by a 2 day treatment-free period. Animals in groups 1 to 5 were treated one week in advance of those in groups 6 to 8.

3.2.5 Method and frequency of test article preparation

Fresh dispersions of the test article were prepared daily at the concentrations specified in section 3.2.3. The material was prepared according to the method supplied by the study sponsor as follows: the test article was melted on a water-bath until the temperature reached 60°C. The molten test article was stirred into water prewarmed to 60°C and agitated with a high speed stirrer.

3.2.6 Proof of absorption of test article

Proof of absorption of the test article by the test system was not requested by the study sponsor.

3.2.7 Stability of test article preparations

No samples for determination of stability were retained.

3.3 Test system

3.3.1 Species/strain/supplier

New Zealand White rabbits were obtained from Morton Commercial Rabbits, Parsonage Farm, Stansted, Essex, or from HLE stock. A total of 8 healthy male and 8 healthy female animals was used.

3.3.2 Justification for the selection of test system

The New Zealand White rabbit was chosen by the study sponsor as the results of percutaneous toxicity tests in rabbits relate well to human hand immersion tests.

3.3.3 Specification

On receipt, all animals were examined for external signs of ill-health or injury. The animals were acclimatised to the conditions within the experimental room for at least 5 days before the start of treatment. Towards the end of acclimatisation the animals were re-examined and their suitability for experimental purposes confirmed.

At the start of treatment, male animals were within the body weight range 2.52-2.93 kg and the females within the range 2.48-3.50 kg.

3.3.4 Husbandry

All animals were housed individually in grid-floor cages in a single experimental room maintained at not less than 12°C (temperature range 13-25°C). A constant artificial photoperiod of 14 hours light (06.00-20.00 hours) and 10 hours darkness was used. The relative humidity was in the range 66-75%.

3.3.5 Diet

Throughout the study the rabbits were given free access to diet.

On arrival and for the first 24 hours the animals were offered Spillers Rabbit Diet (Spillers Agriculture Ltd., Gainsborough, Lincolnshire) which is the diet used by the animal supplier. This diet was replaced by SQC Beta Standard Rabbit diet (BP Nutrition (UK) Ltd., Stepfield, Witham, Essex) within 48 hours of arrival. The Beta rabbit diet was then used throughout the experiment. Tap water was provided ad libitum and dispensed from automatic drinking valves.

3.4 Randomisation

The animals were randomly allocated to treatment groups by means of random permutation tables. Cage positions within the battery were also randomly allocated. Male and female rabbits were randomised separately for both group allocation and cage position.

3.5 Experimental design and identification of the test system

After random allocation to treatment group each animal was permanently identified by metal ear tag, according to the following schedule:

Group number	Colour code	Animal identification numbers Male	Female
1	Buff	6720	6725
2	Green	6721	6726
3	Blue	6722	6727
4	Yellow	6723	6728
5	Pink	6724	6729
6	Buff/2	6790	6793
7	Green/2	6791	6794
8	Pink/2	6792	6795

Each cage was labelled with a group-related coloured card bearing the following information: HLE project number, animal number, sex, test article, date of start of treatment and Home Office licensee.

3.6 Evaluation of effects

3.6.1 Appearance, behaviour and general observations

All animals were examined at least once daily for signs of ill-health or overt toxicity, and any changes were recorded on individual case history sheets.

3.6.2 Body weight

Individual body weights were recorded on the first day of test, and when the animal were killed.

3.6.3 Skin irritation

Skin irritation at the application site was assessed daily, about 24 hours after each application, according to the following scale:

Erythema
- 0 - none
- 1 - slight (barely perceptible)
- 2 - moderate (well defined)
- 3 - severe (beet redness)

Oedema
- 0 - none
- 1 - slight (barely perceptible)
- 2 - moderate (raised approx. 1mm)
- 3 - severe (raised by more than 1 mm)

Atonia (not including eschar area)	0 - normal 1 - slight impairment of elasticity 2 - moderate (slow return to normal) 3 - marked (no elasticity)
Desquamation (not including eschar area)	0 - none 1 - slight scaling 2 - moderate (scabs and flakes) 3 - marked (pronounced flaking with denuded areas)
Fissuring	0 - none 1 - slight (definite cracks in epidermis) 2 - moderate (cracks in dermis) 3 - marked (cracks with bleeding)

Presence of eschar formation and exfoliation.

3.7 Terminal studies

No terminal studies were performed. At the end of the study all animals were killed and discarded.

4. RESULTS

4.1 Clinical observations (Appendix 1)

An increased sensitivity to touch at the test site was noted for 6727F (group 3) on days 3 and 4. Apart from the skin reactions (section 4.3) all animals survived the study in apparent good health.

4.2 Body weight (Appendix 2)

There was no marked effect on body weights during the study although slight reductions in body weight were seen in several animals.

4.3 Skin irritation (Appendix 3)

Irritation of the skin at the application site developed in both animals from group 5 during the first 24 hours after treatment and persisted for the remainder of the study. Treatment was stopped after 2 days. The skin irritation was characterised initially by moderate erythema, oedema and atonia, which developed into marked erythema after the second application of E1069.02 and remained so until day 8. Slight fissuring was noted after 6 days without treatment before the animals were killed.

A reaction to treatment characterised by erythema and fissuring was seen in animals in groups 2, 3 and 4. These animals were treated for 4 days only. A slight reaction was seen 24 hours after the first treatment, this developed into a marked reaction by day 8.

Animals in groups 7 and 8 were treated for 5 and 4 days respectively, and a slight to moderate reaction was observed. Erythema and atonia were seen 24 hours after the first treatment, wrinkled skin occurred with atonia after 2 days of treatment and fissuring occurred after 3 days of treatment.

In all animals treated with E1069.02 a thickening of the epidermis developed at the treatment site. This thick layer of skin lifted in both animals in group 5 and the male of group 4 to reveal large areas of necrosis. The presence of the thick layer of skin prevented assessment of oedema and atonia in many animals.

No reaction to treatment was observed in group 1 and 6 animals.

5. DISCUSSION

Repeated application of E1069.02 at concentrations of 0.5% w/v and above elicited an overt moderate to marked irritant response in the nonabraded skin of the rabbit. The skin reaction seen at a concentration of 0.5% w/v E1069.02 would preclude higher dose levels in subsequent 4 and 13 week percutaneous studies.

6. ARCHIVE

All primary data and specimens will be retained in the HLE archive for 2 years after submission of the final report. At the end of this period we will discuss with the sponsors whether they require storage for a longer period, either at HLE, for which an archiving charge will be made, or in the sponsors' own archive.

Specimens will be taken to include test/control articles, any tissue, tissue block or slides derived from a test system for examination or analysis. Biofluids are specifically excluded from the above definition because of the lability of the constituents.

Primary data will be taken to include laboratory data sheets, records, memoranda notes, photographs, microfilm, computer records that are a result of the original observations and activities of the study and which are necessary for the reconstruction and evaluation of the report of the study.

HLE Project no. 110/365

PROTOCOL COVER SHEET

PROTOCOL AND AMENDMENTS

HARLEQUIN
LABORATORIES EUROPE LTD
Otley Road, Harrogate
North Yorkshire HG3 1PY England

[redacted]

APPENDIX 4

PROTOCOL TITLE A 7 DAY TOPICAL DOSE RANGE-FINDING STUDY IN THE RABBIT

PROTOCOL NUMBER P1385/21/6/-/558/d

PROJECT NUMBER 110/365

TEST ARTICLE E1067.01 [redacted]

SPONSOR [redacted]

Prepared for HLE by pp. D.SHAW. date June 2nd 1981

Authorised for HLE by [redacted]. June 2nd 1981

DR. A.K ARMITAGE, RESEARCH DIRECTOR.

*Authorised for Sponsor by [redacted]

Acknowledged and implemented by Project Manager [redacted] June 11th 1981

*Instruction to Sponsor. Please type your name and company status underneath your signature, and return one signed copy to HLE as soon as possible.

PROTOCOL NUMBER: P1385/21/6/1/558/d

HLE Project number: 110/365

Study Sponsor's Project number: [redacted]

E1067.01: A 7 DAY TOPICAL DOSE RANGE-FINDING STUDY IN THE RABBIT

1. Objective

To determine suitable solution concentrations of the test article in terms of skin irritation, for use in subsequent 4 and 13 week percutaneous toxicity studies.

2. Test/control articles

2.1 Description/identification

The test article will be supplied by the study sponsor, who will also supply the following information:
test article identification number, purity, stability and known hazardous properties. This information will be included in the protocol by completion of an amendment to protocol form.

Information on the composition of the test article is available from the study sponsor but will not be given to HLE to ensure the blind character of this study.

The test articles will be stored as supplied at ambient temperature in the dark.

The control article and vehicle for the test article will be tap water.

2.2 Route/method of administration

As one possible route of human exposure will be contact with skin, the test article will be applied directly to a shaved and non-abraded area of skin (approximately 10 x 10 cm) on the dorso-lumbar region.

All all metal ball-ended cannula and plastic disposable syringes will be used for application.

Animals will be placed in Elizabethan collars for 7 hours each day to minimise ingestion of the test article. Seven hours after treatment collars will be removed and the application sites washed with warm tap water and then blotted dry.

The application sites will be shaved as necessary to maintain the area free of fur. Care will be taken not to damage the skin in the treatment area.

2.3 Dose levels

The volume of test or control article applied to each animal will be calculated on individual body weight at the start of the week.

Group numbers	Control/test articles	Treatment level	Concentration of test article % w/v
1	Tap water	control	N/A
2	Test article in vehicle	low	*
3	Test article in vehicle	intermediate - I	*
4	Test article in vehicle	intermediate - II	*
5	Test article in vehicle	high	*

* To be specified by the study sponsor and issued as an amendment to this protocol.

N/A Not applicable.

2.3.1 Test article

Four concentrations will be employed for the test article, and applied at a treatment volume of 2 ml/kg/day.

2.3.2 Control article

Group 1 animals will be treated with 2 ml/kg/day of tap water only.

2.4 Frequency of administration

Test and control articles will be applied once daily on 5 consecutive days. The animals will then be maintained untreated for a further 2 days.

2.5 Method and frequency of test article preparation

Fresh solutions of the test article will be prepared daily. Surplus test article preparations will be discarded. A detailed method for test article preparation will be supplied by the study sponsor before the start of treatment.

2.6 Proof of absorption of test article

Proof of absorption of the test article by the test system was not requested by the study sponsor.

2.7 Stability of test article preparations

No samples for determination of stability will be retained.

3. Test system

3.1 Species/strain/supplier

A sufficient number of New Zealand White rabbits to provide 5 healthy male and 5 healthy female animals will be obtained from Morton Commercial Rabbits, Parsonage Farm, Stansted, Essex.

3.2 Justification for the selection of test system

The New Zealand White rabbit was chosen by the study sponsor as the results of percutaneous toxicity tests in rabbits relate well to human hand immersion tests.

3.3 Specification

At the start of treatment the animals will be within the body weight range 2.2 - 2.8 kg. On receipt, all animals will be examined for external signs of ill-health and unhealthy animals will be discarded.

Before the start of treatment, animals will be held in the experimental room for about 5 days, towards the end of which the health status of the animals will be reassessed and their suitability for experimental purposes confirmed.

3.4 Husbandry

Experimental animals will be housed individually in grid-floor cages in a single experimental room maintained at not less than 12°C. A constant artificial photoperiod of 14 hours light (06.00-20.00 hours) and 10 hours darkness will be used.

3.5 Diet

Throughout the study the rabbits will have free access to diet.

On arrival and for the first 24 hours the animals will be offered Spillers Rabbit Diet (Spillers Agriculture Ltd., Gainsborough, Lincolnshire) which is the diet used by the animal supplier. This diet will be replaced by SQC Beta Standard Rabbit diet (BP Nutrition (UK) Ltd., Stepfield, Witham, Essex) within 48 hours of arrival. The Beta rabbit diet will then be used throughout the experiment.

Tap water will be provided ad libitum and dispensed from automatic drinking valves.

4. Randomisation

The animals will be randomly allocated to treatment groups by means of random permutation tables.

Cage positions within the battery will be randomised.

Male and female rabbits will be randomised separately for both group allocation and cage position..

5. Experimental design

Group number	Treatment level	Number of animals Male	Female
1	Control	1	1
2	Low	1	1
3	Intermediate I	1	1
4	Intermediate II	1	1
5	High	1	1

Animals will be treated for 5 days and killed after 2 days without treatment.

6. Identification of test system

Each animal will be permanently identified by metal ear tag, according to the following schedule:

Group number	Colour code	Animal identification numbers Male	Female
1	Buff	6720	6725
2	Green	6721	6726
3	Blue	6722	6727
4	Blue/2	6723	6728
5	Pink	6724	6729

7. Evaluation of effects

7.1 Appearance, behaviour and general observations

All animals will be examined at least once daily for signs of ill-health or overt toxicity. Clinical changes will be recorded on individual case history sheets.

Any animal found moribund or dead will be removed for necropsy. Where possible the cause of death or moribund condition will be documented.

7.2 Body weight

Individual body weights will be recorded on the first day of test, and then 7 days later.

7.3 Food consumption

Food consumption will not be determined.

7.4 Water consumption

Water consumption will not be determined.

7.5 Ophthalmoscopy

Ophthalmoscopic examination will not be carried out.

7.6 Skin irritation

Skin irritation at the application site will be assessed daily, about 24 hours after each application according to the following scale:

Erythema	0 - none
	1 - slight (barely perceptible)
	2 - moderate (well defined)
	3 - severe (beet redness)
Oedema	0 - none
	1 - slight (barely perceptible)
	2 - moderate (raised approx. 1mm)
	3 - severe (raised by more than 1mm)
Atonia (not including eschar area)	0 - normal
	1 - slight impairment of elasticity
	2 - moderate (slow return to normal)
	3 - marked (no elasticity)
Desquamation (not including eschar area)	0 - none
	1 - slight scaling
	2 - moderate (scabs and flakes)
	3 - marked (pronounced flaking with denuded areas)
Fissuring	0 - none
	1 - slight (definite cracks in dermis)
	2 - moderate (cracks in dermis)
	3 - marked (cracks with bleeding)

Presence of eschar formation and exfoliation.

8. Laboratory analyses

No laboratory investigations will be performed.

9. Terminal studies

No terminal studies will be performed. At the end of the study all animals will be killed and discarded.

10. Reports

10.1 Incidental reports

The study sponsor will be informed immediately if any toxicologically significant results are obtained during the course of the study.

Additional procedures required to elucidate an observed effect, that incur additional costs, will first be discussed with the study sponsor.

10.2 Interim reports

No written interim reports will be submitted.

10.3 Final reports

The report will be prepared to contain the following information:

1. The objectives and procedures stated in the approved protocol including any changes made to the original protocol.

2. The identity of the test/control substances (by name or code number) and their strength (quality/purity).

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Appendix 4
P1385/21/6/1/558/d

3. The test system - species, strain and sex of the animals used.

4. Procedure for identification of the test system.

5. The dose levels used, the dosage regimen, route of administration and duration of treatment.

6. Any unforeseen circumstances which may have affected the quality or integrity of the study.

7. The reports of the individual scientists involved in the study, e.g. pathologist/statistician.

8. The signature of the project manager and other scientists involved in the study as authentication of the report.

9. The location of all raw data and the final report.

10. The following items of data will be presented:

experimental design

effects on growth, general appearance

clinical observations (toxic and pharmacological effects, conditions and behaviour)

morbidity and mortality

There will be tabular presentations, with appropriate statistical evaluation where necessary of:

skin irritation

body weights

survival data

11. Quality assurance

11.1 Adherence to protocol

HLE undertake to adopt all reasonable measures to record data in accordance with this protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of HLE. All such variations will be documented in the project records, together with the reason for their occurence where appropriate and detailed in the final report.

If major alterations in protocol specifications occur an amendment to protocol will be issued.

11.2 Amendments to protocol

Amendments to the authorised protocol whether instigated by HLE or by the study sponsor will only be made after proper authorisation. This will be achieved by completion of an Amendment to Protocol form by HLE and by the study sponsor. Whenever possible this documentation will be completed before the deviations from the original protocol take effect.

11.3 Standard operating procedure

Unless otherwise specified all procedures mentioned in the protocol are the subject of detailed standard operating procedures.

11.4 Quality assurance evaluation

The study described in this protocol will be subject to quality assurance evaluation. The form of the inspection will be described in the Quality Assurance Unit standard operating procedures.

11.5 Inspection by regulatory authorities

In the event of an inspection by an outside authority during the course of the study, the sponsor will be consulted before the inspectors are permitted access to any of the project records or the experimental areas.

12. Archive

All primary data and specimens will be retained in the HLE archive for 2 years after submission of the final report. At the end of this period we will discuss with the sponsors whether they require storage for a longer period, either at HLE for which an archiving charge will be made or in the sponsors' own archive.

Specimens will be taken to include test/control articles, any tissue, tissue block or slides derived from a test system for examination or analysis. Biofluids are specifically excluded from the above definition because of the lability of the constituents.

Primary ~~data~~ will be taken to include laboratory data sheets, records, memoranda, notes, photographs, microfilm, computer records that are a result of the original observations and activities of the study and which are necessary for the reconstruction and evaluation of the report of the study.

May, 1981.

17.06.81

[redacted]

RECEIVED 13 JUL 1981

BIOLOGICAL TEST FOR SAFETY : [redacted]

...ginator [redacted] Originator's [redacted] ...te [redacted] Originator's AD [redacted]

...ologist [redacted] Name

...mated Total Cost [redacted]

...mated Dates of:

...ilability of Analytical Data 1ST JUNE 1981 Receipt of Report 1ST DECEMBER 1981

Product Coordination Manager [redacted] Date

...e of Test Substance (by Originator) TAMET (ET-BASE) Identification Number E- 1069.02

...bstance required by (date) 1ST JUNE 1981 Agreed by PDF ______ (Initials)

...Completion Date 5TH MAY 1981

		Panel/Blind Test	Ship Test	Test Market	National
...pe of Consumer Exposure(s) for ...ich Safety ...earance is ...quested	No. of Subjects Starting Date Duration Location		OCT 1981 GERMANY		JAN 1982 GERMANY

...fety Test Requirements (by PARS)

...ests:

	Amount of Substance Needed	
√28 Day Perc. Tox.	1 Kg	[redacted]
√91 Day Perc. Tox.	1 Kg	
√91 Day Oral Tox.	1 Kg	
Mutagenicity Screen [redacted]	4 x 100 g	

[redacted]

8TH JUNE 1981
Date

Issue 1 : 17.6.80

[redacted]

2ND MAY 1984

28 Day Percutaneous Toxicity In Rabbits : HLE 2827-110/366 & HLE 2759-110/365

Test Material	Treatment Concentration
Tallow Dihydroxyethylamine "TAMEA" E1069.02	0.1% and 0.5% w/v applied at 2 ml/kg body weight

Two groups comprising five rabbits of each sex were treated topically with aqueous dispersions of E1069.02. The dispersions were applied to non-abraded skin for 5 consecutive days each week for 4 weeks. A third, control group was treated with 2 ml/kg of distilled water.

Repeated topical application of E1069.02 at 0.1 and 0.5% w/v elicited slight and moderate irritant responses respectively. There was no evidence of systemic toxicity from mortalities, clinical changes, haematological measurements, body and organ weights or pathological findings..

[redacted]

[redacted]

.../Cont'd

[redacted]

2ND MAY 1984

[redacted]

Conclusion

TAMET, Tallow dihydroxyethylamine, is a moderate-to severe skin irritant but does not produce any signs of systemic toxicity after a 28-day percutaneous dosing period.

[redacted]

The toxicity of TAMET benzoate is comparable with that of the structurally similar TAPUATE.

[redacted]

[redacted]

[redacted]

TEST SUBSTANCE CHARACTERISATION REPORT [redacted]

A

Test Substance Identification Number E- 1069.02

[redacted]

Originator : [redacted] (Name)

B

Name of Product or Ingredient (or code designation) "TAMET"

Brand Notebook Ref. (including Production code if available) BATCH 4

Physical Form SOLID Colour YELLOW/BROWN Density

Solubility SOLUBLE IN HOT WATER pH (conc) % Sample Expiration Date JANUARY 1982

Recommended Storage Conditions STORE AT ROOM TEMPERATURE

Hazards (i.e. flammability, toxic gases)

C

FORMULATED COMPOSITION

Component (a)	Nominal Level (% by Wt)	Acceptable Range (b)	Stock Code No.	Supplier	Lot Number (b)
B-TALLOW DI 2-HYDROXYETHYL AMINE "TAMET"	-	-	-	AKZO CHEMIE	BATCH 4

(a) Ingredients will be listed by chemical name: non-chemical names such as Tergitol 15-3-9 or Yellow Dye D&C No. 10 may be acceptable but should be previewed with the responsible toxicologist. Chemical names which are inconveniently long may be abbreviated in tables but should be listed in full in referenced footnotes. Non-definitive identifications (e.g. Arquad, BC-base) are not acceptable).

(b) If information requested is not known then the symbol NK will be entered.

The above information provided by:

Process Development Person (PDP) [redacted] (Name) (signature) [redacted]

[redacted] ANALYTICAL REQUEST FORM

D

Please carry out the following analyses according to your recorded procedures. This data is needed for non-clinical safety studies.

Signed _____ (Name), Date _____

Agreed for Analytical Section _____ (Name), Date _____

Agreed for Human Safety _____ (Name), Date _____

Date Submitted	Submitter Code	Component or Property	Measured Value	Analytical Notebook Ref
		$CaSO_3$	22.96	
3.2.81	4/785 :	1^o AMINE meq/g	0.01	1725/19
		2^o AMINE meq/g	0.02	
		3^o AMINE meq/g	2.754	
		AMMONIA	0.01	
		ASH	NIL	
		VOLATILES	1.60	
		NONIONICS	1.46	
		OH VALUE	55.1	
		LOVIBOND COLOUR (R)	2.5	
		(Y)	8.3	

1682/103

GLC : CHAINLENGTH DISTRIBUTION $C_{12}E_2$ 1.5; $C_{14}E_2$ 3.0; $C_{15}E_2$ 1.0; $C_{16}E_2$ 0.2; $C_{16}E_2$ 34.2; $C_{17}E_2$ 1.9; $C_{18}E_2$ 2.2; $C_{18}E_2$ 51.7; $C_{16}E_3$ 1.4; $C_{18}E_3$ 2.2; C_2O E_2 0.7.
AV. MW. 344

Analytical information verified by: [redacted] (Name) _____ (signature) 27/5/81 (Date)

E

This test substance is suitable for non-clinical safety testing

Originator's [redacted] (signature) 27/V/81. (Date)

Toxicologist [redacted] (Name) _____ (signature) 27/5/81 (Date)

TEST SUBSTANCE CHARACTERISATION REPORT [redacted]

Test Substance Identification Number E- 1085.01

[redacted]

Principal Investigator [redacted] (Name)

Name of Product or Ingredient (or code designation) "TAMET"/BENZOATE SOLUTION

Brand Notebook Ref. (including Production Code if available) [redacted]

Physical Form LIQUID Colour PALE BROWN/YELLOW Density 1000g/l

Solubility _____ pH (conc) _____ Sample Expiration Date MARCH 1982

Recommended Storage Conditions STORE AT ROOM TEMPERATURE; 20°C

Hazards (i.e. flammability, toxic gases) _____

FORMULATED COMPOSITION

Component[a]	Nominal Level (% by Wt)	Acceptable[b] Range	Stock Code No.	Supplier	Lot Number[b] (NB-Ref)
[redacted]ALLOW B-DIHYDROXYETHYL AMINE	14.9		-*	GOLDSCHMIDT	BATCH 1834
BENZOIC ACID	5.1		60064	NK	NK(SAMPLE RETAINED)
DISTILLED WATER	80		-	-	-

*STOCK CODE NO. 70308 ONLY SO FAR GIVEN FOR TAMET MATERIAL FROM AKZO CHEMIE (SUPPLIER)

[a] Ingredients will be listed by chemical name: Non-chemical names such as Tergitol 15-3-9 or Yellow Dye D&C No. 10 may be acceptable but should be previewed with the responsible toxicologist. Chemical names which are inconveniently long may be abbreviated in tables but should be listed in full in referenced footnotes. Non-definitive identifications (e.g. Arquad, BC-base) are not acceptable.

* information requested is not known then the symbol NK will be entered.

[redacted]bove information provided by:

Originator [redacted] (Signature) 11th September 1981

(Name) (Date)

D

[redacted] ANALYTICAL REQUEST FORM

Please carry out the following analyses according to your recorded procedures. This data is needed for non-clinical safety studies.

Signed _____ (Name) [redacted] Date _____

Agreed for Analytical Section [redacted] Date _____

Agreed for Human Safety _____ (Name) Date _____

Date Submitted	Submitter Code	Component or Property	Measured Value	Analytical Notebook Ref
3-8-81	4/842D	Cat SO_3 Equiv.	2.913	
		TERTIARY Amine	2.831	
		SECONDARY Amine	0.022	
		PRIMARY Amine	0.021	1725 p.131 & 1599 p.142
		Ash	0.017	
		Volatiles	0.22	
		Nonionics	1.38	
		Lovibond RED	1.2	
		YELLOW	3.7	

GLC:- Chainlength Distribution (%)

$C_{10}E_2$ 0.3; $C_{12}E_2$ 1.6; $C_{14}E_2$ 4.4; $C_{15}E_2$ 0.5; $C_{16}E_2$ 29.9; $C_{17}E_2$ 1.5; $C_{18}E_2$ 2.3; $C_{16}E_2$ 54.4; $C_{20}E_2$ 0.9; $C_{16}E_3$ 1.2; $C_{18}E_3$ 2.0 UNKNOWN 1.0

Av. MW = 343

Analytical information verified by: [redacted] (signature) 11th September 1981 (Date)

E

This test substance is suitable for non-clinical safety testing

Originator's [redacted] (signature) _____ (Date)

Toxicologist: [redacted] (signature) 11 September 1981 (Date)

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: December 18, 2014

SUBJECT: Analytical Information on the PEG-2 Tallow Amine Tested in the Oral Toxicity Study in Rats Submitted October 31, 2014

The attached was included among the appendices of the following reference which was provided to CIR on October 31, 2014.

13 Week Oral (Dietary) Toxicity Study in the Rat ECM BTS 306, E1095.01. Hazleton Laboratories Europe LTD. February 1982.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Analytical Info w/ 90 day rat study

TSCR ANALYTICAL REQUEST FORM

D

Please carry out the following analyses according to your recorded procedures. This data is needed for non-clinical safety studies.

Signed _____ (Name), Date _____

Agreed for Analytical Section _____ (Name), Date _____

Agreed for Human Safety _____ (Name), Date _____

Date Submitted	Submitter Code	Component or Property	Measured Value	Analytical Notebook Ref
		$CatSO_3$	22.96	
3.2.81	4/785 :	1^o AMINE meq/g	0.01	1725/19
		2^o AMINE meq/g	0.02	
		3^o AMINE meq/g	2.754	
		AMMONIA	0.01	
		ASH	NIL	
		VOLATILES	1.60	
		NONIONICS	1.46	
		OH VALUE	55.1	
		LOVIBOND COLOUR (R)	2.5	
		(Y)	8.3	

GLC : CHAINLENGTH DISTRIBUTION $C_{12}E_2$ 1.5; $C_{14}E_2$ 3.0; $C_{15}E_2$ 1.0; $C_{16}E_2$ 0.2; $C_{16}E_2$ 34.2; $C_{17}E_2$ 1.9; $C_{18}E_2$ 2.2; $C_{18}E_2$ 51.7; $C_{16}E_3$ 1.4; $C_{18}E_3$ 2.2; C_2O E_2 0.7.
AV. MW. 344

1682/103

Analytical information verified by: [redacted]

E

This test substance is suitable for non-clinical safety testing

Originator's [redacted] (signature) 27/V/81. (Date)

Toxicologist: [redacted] (signature) 27/5/81 (Date)

Test Substance Identification Number E- 1095.01 [redacted]

[redacted]

Principal Investigator [redacted]
(Name)

Name of Product or Ingredient (or code designation) "TAMET"/BENZOATE SOLUTION

Brand Notebook Ref. (including Production Code if available) [redacted]

Physical Form LIQUID Colour PALE BROWN/YELLOW Density 1000g/l

Solubility _____ pH (conc) _____ Sample Expiration Date MARCH 1982

Recommended Storage Conditions STORE AT ROOM TEMPERATURE; 20°C

Hazards (i.e. flammability, toxic gases) _____

FORMULATED COMPOSITION

Component[a]	Nominal Level (% by Wt)	Acceptable Range[b]	Stock Code No.	Supplier	Lot Number[b] (NB-Ref)
[illegible]ALLOW B-DIHYDROXYETHYL AMINE	14.9		-*	GOLDSCHMIDT	BATCH 1834
BENZOIC ACID	5.1		60064	NK	NK(SAMPLE RETAINED)
DISTILLED WATER	80		-	-	-

*STOCK CODE NO. 70308 ONLY SO FAR GIVEN FOR TAMET MATERIAL FROM AKZO CHEMIE (SUPPLIER)

(a) Ingredients will be listed by chemical name: Non-chemical names such as Tergitol 15-3-9 or Yellow Dye D&C No. 10 may be acceptable but should be previewed with the responsible toxicologist. Chemical names which are inconveniently long may be abbreviated in tables but should be listed in full in referenced footnotes. Non-definitive identifications (e.g. Arquad, BC-base) are not acceptable.

(b) If information requested is not known then the symbol NK will be entered.

The above information provided by:

DRD Originator [redacted]
(Name) (Date)

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 7, 2015

SUBJECT: Tertiary Amine Content of PEG Fatty Acid Amine Ingredients

A supplier reports that they produce the following PEG fatty acid amine ingredients under well formulated and controlled conditions so that the tertiary amine specifications are all greater than or equal to 95%.

PEG-2 Cocamine
PEG-5 Cocamine
PEG-2 Hydrogenated Tallow Amine
PEG-5 Tallow Amine
PEG-5 Stearamine

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 14, 2015

SUBJECT: Summaries of Sensitization Studies PEG-2 Hydrogenated Tallow Amine

Hill Top. 1978. Summary of a delayed contact hypersensitivity study of PEG-2 Hydrogenated 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 Hydrogenated Tallow Amine did not induce sensitization in guinea pigs.

MB Laboratories. 2002. Local lymph node assay of PEG-2 Hydrogenated 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 Hydrogenated 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 Hydrogenated 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 Hydrogenated 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 Hydrogenated Tallow Amine, the magnitude of the proliferative response and the activation state of cells localized in the nodes of treated mice identify PEG-2 Hydrogenated Tallow Amine as a potential dermal sensitizer.

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

Personal Care Products Council
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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: January 14, 2015

SUBJECT: Composition PEG-2 and PEG-5 Cocamine

A supplier reports that their PEG-2 and -5 Cocamine products are composed of 97-100% tertiary amine. They contain:

a. Less than 0.5% secondary amine
b. Less than 50 ppb nitrosamine
c. Residual moisture

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: February 5, 2015

SUBJECT: PEG-5 Soyamine

Anonymous. 2007. Forearm open application patch test of a hair dye formulation containing 3.4% PEG-5 Soyamine.

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[redacted]

FOREARM OPEN APPLICATION PATCH TEST

STUDY NO. [redacted]

Hair dye formulation containing
3.4% PEG-5 Soyamine

[redacted]

[redacted]

PERFORMED BY:

[redacted]

[redacted]

FOREARM OPEN APPLICATION PATCH TEST

[redacted]

TEST SUBSTANCE IDENTIFICATION [redacted]

CONCENTRATION: 100%, As Is

VEHICLE: Not Applicable

PREPARATION OF TEST MATERIALS: See following pages for mixtures of test materials

SUMMARY:

Under the conditions of this modified forearm open application patch test (one 30 minute exposure), results indicate minimal to moderate irritation to the test products at the 30 minute and 1 hour post exposure grade period. All treatment sites had resolved to "0" by the 24 hour grading period.

Individual grades can be found in Table I.

Submitted by: [redacted] 8Feb07
Date

Approved by: [redacted] 2-8-07
Date

[redacted]

PURPOSE: To confirm that increased peroxide/persulphate concentrations do not increase irritation potential.

INVESTIGATIVE FACILITY: [redacted]

TEST LOCATION: [redacted]

INVESTIGATOR: [redacted]

STUDY MANAGER: [redacted]

STUDY COORDINATOR/GRADER: [redacted]

SPONSOR AND MONITOR: [redacted]

TEST DATES: 1/25 – 1/26/07

NUMBER OF PANELISTS COMPLETING THE STUDY: 12

[redacted]

PROTOCOL:

The study protocol, [redacted]: Forearm Open Application Patch Test, was followed with the modifications or deviations cited below. See Appendix I for the complete protocol.

DEVIATIONS/MODIFICATIONS TO PROTOCOL:

The procedure of applying test materials to the forearm occurred only one time; grading was performed at 30 minutes, 1 hour, and 24 hours post exposure.

SUBJECT INFORMATION:

Number of subjects screened/excluded at initial interview:	12/0
Number of subjects starting study:	12 (10 females/2 males)
Number of subjects who withdrew:	0
Miscellaneous information:	None

RECORD OF MONITORING VISITS: This study was not monitored.

[redacted]

TEST MATERIAL INFORMATION:

Treatment A Identification Number:	[redacted]
Treatment A did not contain PEG-5 soyamine	[redacted]
Color:	Blue
Physical Form:	Cream
Concentration Tested:	100%, As Is
Concentration Relative to Use Concentration:	1x
Vehicle:	Not Applicable
Test Material Preparation:	[redacted]
Patch Type:	Not Applicable
Amount Placed on Forearm:	0.5 ml
Method of Application:	Pipette into center of pre-marked site
Patch Site:	Inner forearm

ADVERSE EVENTS: None

[redacted]

TEST MATERIAL INFORMATION:

Treatment B Identification Number:	Mixture: [redacted]
Treatment B did not contain PEG-5 soyamine	
Product Name:	[redacted]
Color:	Blue
Physical Form:	Cream
Concentration Tested:	100%, As Is
Concentration Relative to Use Concentration:	1x
Vehicle:	Not Applicable
Test Material Preparation:	[redacted]
Patch Type:	Not Applicable
Amount Placed on Forearm:	0.5 ml
Method of Application:	Pipette into center of pre-marked site
Patch Site:	Inner forearm
ADVERSE EVENTS:	None

[redacted]

TEST MATERIAL INFORMAITON

Treatment C Identification Number:	Mixture of [redacted] Developer, Tint, and Activator
Product Name:	[redacted] 6% Peroxide Developer, [redacted] Lightener Tint [redacted] 14% Sulfate Powder Sachet
Color:	Off-White Tint contains 11% PEG-5 soyamine
Physical Form:	Cream
Concentration Tested:	100%
Concentration Relative to Use Concentration:	1x
Vehicle:	Not applicable
Test Material Preparation:	Mix 1 bottle of [redacted] 6% Peroxide Developer [redacted], 1 tube of [redacted] Lightener Tint [redacted] & 1 packet of [redacted] 14% Sulfate Powder Sachet [redacted] Bottle = 3.75 oz., tube = 2.0 oz., powder = 0.8 oz. PEG-5 soyamine applied concentration is 3.4%.
Patch Type:	Not Applicable
Amount Placed on Forearm:	0.5 ml
Method of Application:	Pipette into center of pre-marked site
Patch Site:	Inner forearm

ADVERSE EVENTS: None

[redacted]

RESULTS:

Table I
Individual Panelist Scores

Pan #	Tx.	Grade 30 Min Post Exposure	Grade 1 Hour Post Exposure	Grade 24 Hr Post Exposure
1	[redacted]			
	C	0	0	0
2	[redacted]			
	C	0	0	0
3	[redacted]			
	C	0.5	0	0
4	[redacted]			
	C	0	0	0
5	[redacted]			
	C	0	0	0
6	[redacted]			
	C	0	0	0
7	[redacted]			
	C	1	1	0
8	[redacted]			
	C	0	0	0
9	[redacted]			
	C	0	0	0
10	[redacted]			
	C	0	0	0
11	[redacted]			
	C	0	0	0
12	[redacted]			
	C	0	0	0

APPENDIX I

[redacted]

Forearm Open Application Wash Test

Revision #:	**2**	**Procedure #:**	[redacted]
Supersedes:	[redacted]	**GMDB #:**	
Originator:	[redacted]	**Issue Date:**	[redacted]

1.0 PURPOSE

1.1 To assess the mildness/irritancy of up to six test materials using a forearm controlled open patch application.

2.0 SCOPE

2.1 This protocol is for [redacted] and must be used for all Forearm Open Application Wash Tests.

3.0 REFERENCES

3.1 None.

4.0 RESPONSIBILITY

4.1 It is the responsibility for the person performing the Forearm Open Application Wash Test to follow this SOP.

5.0 PROCEDURE

5.1 Test Materials/Equipment:

5.1.1 Up to 6 beakers – 250 ml.

5.1.2 Cotton tip applicators

5.1.3 Paper towels

5.1.4 Rubber gloves

5.1.5 Mettler or othe appropriate balance and multi-magnestir

5.1.6 Elbow Crease Wash Test Grade Scale (0-4)

5.2 Test Samples:

Prepare 100 mls of each test solutions at the use concentration designated on the skin lab placement form (usually 10 – 100 x usage concentration). Fresh solutions are prepared daily and maintained at ambient temperature.

5.3 Panclists:

5.3.1 At least 12 healthy adult volunteers between the ages of 18 and 65 are required. Eligibility of a volunteer is determined upon completion of a questionnaire (see Attachment I). A volunteer is rejected if he/she has been on an elbow crease wash test within the last two months, meets one of the exclusion criteria (Attachment II), or has a skin condition such as sunburn, acne, skin disease, abrasions, scar tissue, tattoos or active skin disease at the test application site.

5.3.2 Informed Consent:

Each subject participating in the study must read and sign an informed consent sheet (see Attachment III). This sheet will provide a fair explanation of the procedures to be followed, a description of the attendant discomforts and risks, and a description of benefits to be expected, if any. In addition, the subject must be given the opportunity to discuss any procedures involved in the test and be given the opportunity to withdraw his/her consent and to discontinue participation in the test at any time and for any reason.

5.3.2 Instructions:

In written form, the subject is provided with the details involving his/her participation in the test including scheduled visits and procedures to follow if adverse reactions are experienced (see Attachment IV).

5.4 Procedure:

5.4.1 A minimum of twelve panelists will be randomly assigned to a treatment regimen.

5.4.2 Before initial grading, up to four test application areas (approximately 1.25" diameter) will be marked on the volar surface of the subject's left forearm using a template and laboratory marking pen.

5.4.3 Baseline visual grades are obtained at each test site according to the patch test grading scale (Attachment V).

5.4.4. The clinician will dispense 0.5 ml of test material into the center of the skin test site. (Rubber gloves may be worn by the clinician).

5.4.5 Using a cotton tipped applicator, the test solution is evenly distributed over the entire test site for ten (10) seconds.

5.4.6 The above procedure (Steps 3-5) will be repeated on the remaining application areas, moving down the arm towards the wrist. A clean applicator swab is used for each panelist and test material.

5.4.7 Each test solution remains on the skin for 15 minutes or other designated time specified on the test placement form.

5.4.8 Following the specified exposure duration, the subject will rinse the skin site for 30 seconds under running tap water.

5.4.9 After all sites have been rinsed, the subject will gently pat the forearm dry with a disposable towel.

5.4.10 If more than four products are used, the above procedures will be repeated using the right arm.

5.4.11 The entire washing procuedure will be repeated once a day for four consecutive days (Monday – Thursday).

5.5. Grading:

5.5.1 The grading is done by an individual who is familiar with the evaluation of skin reactions. Each site is graded by a qualified visual grader according to the 24-hour repeat patch test grading scale (see Attachment V). Each site is graded before each treatment, one hour and twenty-four hours after treatment. During the exposure period, if the skin site becomes inflamed or reddened, the grader may initiate an additional grading period to occur during the treatment exposure. The grades are recorded in a systematic way in the laboratory notebook.

5.5.2 If the skin grade at a test site reaches a grade of 2.0 or higher, that treatment is discontinued for the remainder of the study. The test site is graded to completion of this test and a score of 2.0 or the actual grade (whichever is higher) is used to evaluate the data. If a subject has a grade of 2.0 or higher on any test sites at the conclusion of the test, he/she will be asked to return ot the laboratory daily for observation until the grade falls to 1.0 or lower. If a subject receives a grade of 3.0 on any test site, he/she will be sent to the Medical Department for appropriate treatment.

5.6 Analysis of Data:

5.6.1 To analyze the results and identify a statistically significant difference ($p \leq 0.05$), the evaluation is made by an analysis of variance (ANOVA) which accounts for variability among individual subjects and between treatment groups prior to treatment. Post treatment analysis is conducted by an ANOVA which accounts for differences in initial evaluations. Least Squares means (LS Mean) are computed for each treatment and compared using a t-test. (Refer to SOP [redacted] (2 treatments) [redacted] (3 treatments). [redacted] (4 treatments) for instructions on using SAS program.)

5.6.2 Considerable caution must be utilized in applying statistics to small base studies.

5.7 Changes in Protocol:

If changes or modifications in the approved protocol are requested, the revisions and reasons for change are to be documented on the [redacted]. The study placement form is to become part of the permanent file for that study. Similarly, the Principal Investigator is to be notified as soon as possible whenever an event occurs that is unexpected and may have an effect on the validity of the study.

[redacted]

[redacted] Toxicologist: [redacted] Date: 5-Dec-06

Alternate Toxicologist: [redacted] Date: 5-Dec-06

6.0 ATTACHMENTS / DEFINITIONS

Attachment #	Description
I	Questionnaire for [redacted] Test Participants
II	Exclusion Criteria for Skin Irritation Testing
III	Voluntary Consent Statement and Test Description
IV	Panelist Instruction Sheet – Forearm Open Application Wash Test
V	Grading Scale

7.0 UPDATE

7.1 Converted [redacted] to new SOP Format.

7.2 Converted to new protocol numbering system (managed from [redacted]).

Revision #2 Updates:

7.3 Consent Form (Attachment III) modified to include panelist rights as outlined in the HIPAA Privacy Act.

7.4 Instruction Sheet (Attachment IV) modified to outline daily compensation for panelist participation.

7.5 Data Analysis section modified to reference SOP # [redacted] (Use of PC-SAS to Analyze Skin Lab Data).

7.6 Converted to global numbering system.

8.0 APPROVALS

Originator	**Date**
Quality Assurance	**Date**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 21, 2015

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

Key Issues

Discussion - Please revise the statement concerning 1,4-dioxane and ethylene oxide from "to remove impurities" to "to limit impurities".

The list of data requests presented in the post-meeting announcement differs from the list of data needs included in the tentative report. The data needs included in the post-meeting announcement were sent to suppliers after the December 2014 CIR Expert Panel meeting.

Additional Comments

Introduction - When it is first mentioned, please indicate that the CIR SSC is a Committee of the Personal Care Products Council.

The HPV summaries should also be mentioned in the Introduction.

Definition and Structure - Please delete the word "tentatively" when discussing the CIR Expert Panel's decision to include other structurally related ingredients in this report.

PEGs Soyamine - Please include a description of the fatty acid carbon chain lengths found in fatty acids derived from soy.

PEG-2 Rapeseedamine - Please include a description of the fatty acid carbon chain lengths found in fatty acids derived from rapeseed oil.

Impurities/Constituents - Please indicate in the text that suppliers have reported that these ingredients are greater than 95% tertiary amines.

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Cosmetic Use - Please also state the maximum leave-on concentration for PEG-2 Oleamine (0.16% in moisturizing products).

Non-cosmetic Use - The summary of safety information for polyoxyethyleneamine tallow amine should not be in the Non-Cosmetic Use section.

If the maternal NOAEL was 15 mg/kg/day, how can the developmental NOAEL of 300 mg/kg/day be the "lowest dose tested"? Perhaps 300 mg/kg/day was the highest dose tested.

Toxicokinetics - "with no mortality" should be deleted from the summary of the Toxicokinetics section.

Metabolism (after figures) - "biotransformations predicted where" needs to be corrected to "biotransformations predicted were"

Analog Toxicity Data Review - Although helpful to the CIR Expert Panel, the Appendix of HPV summaries is unlikely to be published in the *International Journal of Toxicology* as the summaries are already available on the internet.

The three complete studies that were provided by the Council on October 31, 2014 should be mentioned in this section.

Summary - As some of the ingredients not reported to be used have fatty acids from sources other than coconut oil, please use a more general term than "PEGs-cocamine ingredients".

Something is missing from the first sentence of the last paragraph of the Summary. It currently says: "An evaluation of one PEG-4 cocamine structure using the TIMES® indicated..."

Conclusion - The ingredients not in use among the insufficient data ingredients also need to be indicated with asterisks.

Table 3 - The safety test results for PEG-5 Oleamine, PEG-15 Oleamine and PEG-10 Stearamine need to be removed from Table 3, Supplier specifications.

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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: January 29, 2015

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

As part of the preparation of a manuscript on the read-across approach on PEG cocamines for publication, further research on CAS numbers and structures was completed. The following corrections should be made in the tentative report. Please be sure the names and CAS RNs are also corrected throughout the CIR document, to insure that they correspond to the corrections in the analogue tables.

Figures 1-4 - As 18 carbons predominate in fatty acids in tallow, structures of tallow-derived ingredients should be represented by an 18 carbon chain.

Figure 2, 3,4 - PEG-8 Stearamine is a more appropriate name for PEG-8 Hydrogenated Tallowamine.

Figure 3, 4 - The CAS number for PEG-10 Cocamine should be 61791-14-8 (generic) rather than 56049-72-0.

Figure 4 - The CAS number for PEG-15 Cocamine should be 61491-14-8 (generic) rather than 61791-26-2. The CAS number for PEG-15 Tallow Amine should be 61791-26-2 (generic) rather than 65322-67-0.

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Memorandum

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

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: January 29, 2015

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

The CIR Science and Support Committee (CIR SSC) appreciated the discussion at the December 2014 CIR Expert Panel meeting concerning the use of read-across approaches, and we are encouraged by the CIR Expert Panel's willingness to use this approach to help support the safety of ingredients in this report with PEG> 5. The CIR SSC offers the following comments on the tentative report on PEG Cocamines and related ingredients.

After further investigation, an EPA risk assessment (attached) provides a structure for tallow amino phosphate ester (CAS No. 68308-48-5) showing that it is a secondary amine (rather than the structure shown in Figures 2 and 3 of the CIR report) . Assuming that the EPA structure is accurate, this substance should be considered an unsuitable analog and should be removed from the CIR report.

Despite the Dictionary definitions of PEG Cocamines and related ingredients, the Definition and Structure section is correct when it states that "The PEGs Cocamine are a series of tertiary amines". This is supported by information from suppliers in Table 2 that indicate that PEG-2 Cocamine is 97% minimum tertiary amine and PEG-15 Cocamine is 96% minimum tertiary amine. It is also supported by additional information from suppliers provided after the tentative report was prepared, and by composition information provided for the material tested in two studies on PEG-2 Tallow Amine (composition information not yet presented in the report). Therefore, the CIR report should include a discussion of the discrepancy between the Dictionary definitions of these ingredients that indicates that x+y is the average value of the number in the name, and the information from suppliers and the analytical work that indicates that these ingredients (including the ingredients with PEG ≤5) are primarily tertiary amines. Rather than asking for additional information on the composition of the smaller PEG fatty acid amine

ingredients, the CIR Expert Panel should clearly state that their conclusion is for material that is primarily tertiary amines as indicated by the suppliers.

There is a 28-day dermal toxicity study and genotoxicity data (Ames (-), *in vivo* mouse micronucleus assay (-)) on PEG-2 Tallowamine (tallow bis (2-hydroxyethyl) amine (primarily C16-18)). Although the CIR Expert Panel may not consider it appropriate to read-across using dermal toxicity data and genotoxicity data from PEG-2 Tallow Amine to PEG-2 Cocamine (primarily C12 and C14) and PEG-2 Lauramine (C12), we request that the CIR Expert Panel reconsider using read-across from dermal toxicity and genotoxicity data on the tallow ingredients to the following ingredients in the report: PEG Oleamine ingredients (C18 with one double bond), PEG-2 Rapeseedamine (the CIR report on plant oils indicates that rapeseed oil also contains fatty acid that are predominantly 18 carbons long (12.1-57.4% oleic acid (18:1); 11.4-22.1 linoleic acid (18:2)); and other ingredients containing primarily fatty acids with 16-18 carbon chains (Hydrogenated Tallow Amine, Soyamine, Stearamine, Tallow Amine).

The primary use of these ingredients such as PEG-2 Oleamine and PEG-2 Rapseedamine, both known to be irritants, is in hair dye products. Because of the limited dermal exposure to ingredients in hair dyes and the requirement to complete patch tests before use on hair dyes, we think sensitization data on PEG-2 Oleamine and PEG-2 Rapeseedamine to support safe use in hair dyes is unnecessary. We request that the CIR Expert Panel consider a limited conclusion for the smaller PEG tertiary fatty acid amines with fatty acid chain lengths of 16-18, such as PEG-2 Oleamine and PEG-2 Rapeseedamine, of safe for use in hair dye products. Additional sensitization data would be needed to support the safety of these ingredients if used in other cosmetic product categories.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 04/13/10

SUBJECT: **Phosphate Ester, Tallowamine, ethoxylated.** Human Health Risk Assessment to Support Proposed Exemption from the Requirement of a Tolerance When Used as Inert Ingredients in Pesticide Formulations.

PC Code: 900964
Decision No.: N/A
Petition No.: 8E7477
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID Nos.: 4760701, 47600702, 47600703, 47600704, 47600705, 47600706, and 47600707

DP Barcode: N/A
Registration No.: NA
Regulatory Action: Inert Tolerance Exemption
Case No.: NA
CAS No.: 68308-48-5
40 CFR: 180.920

FROM: Alganesh Debesai Alganesh Debesai 4/13/10
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505P)

TO: PV Shah, Chief
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505P)

OVERVIEW

The petitioner, Huntsman Corporation requested that a tolerance exemption be established for Phosphate Ester, Tallowamine, ethoxylated (CAS Reg. No. 68308-48-5) under 40 CFR 180.920 at a maximum of 20% by when used as an inert ingredient in pesticide formulations applied to growing crops as required under the Food Quality Protection Act (FQPA). The purpose of this document is to assess the risk to human health and the environment for the proposed exemptions. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate and ecotoxicity of Phosphate Ester, Tallowamine, ethoxylated. For ease of reading throughout this document Phosphate Ester, Tallowamine, ethoxylated (CAS Reg. No.68308-48-5) is referred to as PETAE.

EXECUTIVE SUMMARY

Huntsman Corporation has submitted a petition (8E7477) requesting a tolerance exemption for PETAE (CAS Reg. No. 68308-48-5) when used as an inert ingredient as a surfactant applied to growing crops under 40 CFR 180.920 at a maximum of 20% in pesticide formulations. EPA published the Notice of Filing for this petition in the Federal Register on April 8, 2008 (74 FR 15975). No comments were received in response to this notice.

The subject product is described as Phosphate Ester, Tallowamine, ethoxylated (CAS Reg. No. 68308-48-5), the primary reactants of which are phosphoric acid and tallow amine ethoxylate (TAE). The product is manufactured with purity greater than or equal of 95%. Consequently the product may contain up to 5% impurities, predominately composed of free phosphoric acid and tallow amine ethoxylated. The free impurities in PETAE are not likely to impart significant toxicity to the product. At biological pH values, other than those in the stomach, the impurities will be present in their dissociated form. Phosphoric acid is a severe eye, skin irritant and has an LC_{50} > 0.85 mg/l by inhalation and is a category IV for oral toxicity with an LD_{50} of 1530 mg/kg (rat) [HSDB 2009].

The toxicological database is adequate to support the use of PETAE when used as inert ingredient. The toxicity data available on the PETAE consists of one OPPTS Harmonized Guideline 870.3650 combined repeated dose toxicity study with the reproduction/development toxicity screening test (rat); acute oral, dermal, inhalation skin irritation and sensitization, and eye toxicity data. The other studies were bridged from alky amine polyalkoxylates (AAPs) since PETAE is a phosphate ester form of alky amine polyalkoxylates (AAPs) which have been recently assessed by the Agency.

The acute oral LD_{50} for PETAE in rats is 550 mg/kg/day (Category III). It has a low acute dermal and inhalation toxicity (Category IV). It is extremely irritating to the eyes of rabbits (Category I) and slightly irritating to the skin (Category IV). It is not a skin sensitizer. In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, clinical signs of toxicity (abnormal respiratory sounds, dyspnea, piloerection, and emaciation), mortality and decreased food consumptions and decreased in body weights were observed in parental animals at 200 mg/kg/day. The clinical sign observed is indicative of local irritation. No effects on Functional Observation Battery (FOB) parameters were observed. The gestation index was decreased primarily due to mortality of females. Decreased in corpora lutea and implantation sites were observed at the highest dose tested (200 mg/kg/day). Decrease in pups body weight gain was observed on day 4 at the high dose only. No mutagenicity studies are available on PETAE, however, there was no evidence that AAPs are mutagenic or clastogenic. There are no chronic toxicity or carcinogenicity studies available in the database. There is no evidence that the AAPs are carcinogenic.

The Agency used a qualitative structure activity relationship (SAR) database, DEREK11, to determine if there were structural alerts for a representative large molecule, as well as a smaller molecule that had been extensively dealkylated, with the amine group intact. No structural alerts were identified. Therefore, there are no triggers for carcinogenicity of PETAE in the database.

The primary route of exposure to PETAE from its use as an inert ingredient in pesticide products applied to growing crops would most likely be through consumption of food to which pesticide products containing PETAE as an inert ingredient have been applied, and possibly through drinking water. Residential (dermal and inhalation) exposures are also possible from the use of home garden pesticide products containing PETAE as an inert ingredient.

Sufficient data were provided on the chemical identify of the PETAE, however, limited data are available on the metabolism and environmental degradation of the PETAE; further, no residue data were provided. The Agency relied collectively on information provided on the representative chemical structures, the generic cluster structures, the submitted physicochemical EPI Suite™ data, structure-activity relationship information, as well as information on other surfactants and chemicals of similar size and functionality to determine the residues of concern for this group of inert ingredients.

There was no hazard attributable to a single exposure seen in the toxicity database for PETAE. Therefore, PETAE is not expected to pose an acute risk.

A chronic aggregate risk assessment takes into account exposure estimates from chronic dietary consumption of food and drinking water. In the absence of actual residue data for PETAE, the Agency performed a dietary (food and drinking water) exposure assessment for PETAE for the proposed pre-harvest use using worst case assumptions. A chronic population adjusted dose (cPAD) of 0.33 mg/kg/day was based on the NOAEL of 100 mg/kg/day which was utilized from systemic toxicity derived from the reproductive and developmental toxicity study in rats and a safety factor of 300 (10x for interspecies and 10x for intra-species variations) and additional 3X FQPA safety factor for the lack of chronic studies was used. The dietary exposure was calculated as a percentage of the cPAD. The chronic dietary estimate for the U.S. Population was 23.2% (children 1-2 yrs were the most highly exposed population with a chronic exposure estimate occupying 75.6% of the cPAD). The complete dietary exposure and Risk assessment results are included in appendix C.

The Agency evaluated residential handler and post application risks for high-end residential exposure scenarios. The combined margins of exposure (MOEs) for all the residential handler scenarios were above 300, and therefore, did not demonstrate a risk of concern to the Agency.

Short-term and intermediate-term aggregate risks, which combined high end residential exposure with average food and drinking water exposures, were not of concern. Acute and long-term (chronic) aggregate risks that included food and water only, were not of concern.

Occupational handler risks are not of concern for all scenarios. RD notes that the occupational handler assessment assumes that mixer/loader/applicators who are handling pesticides containing the PETAE for aerial and ground application on high acreage crops or turf will wear chemical-resistant gloves. RD believes this is a reasonable assumption given the volume of pesticide handled for these applications.

Occupational post application handler risks exceed an MOE of 300 on the day of application for all scenarios.

PETAE is an alkyl phosphate ester that is expected to have a net charge of zero at ambient pHs. It is therefore considered to behave as a neutral molecule, having a low solubility in water, a low volatility and a high K_{OC}. Based on its estimated physical and chemical properties, PETAE does degrade quickly in the environment. It is therefore not expected to be persistent in air, water, soil or sediments. PETAE has a low potential to accumulate in organisms.

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

Taking into consideration all available information on PETAE, it has been determined that there is a reasonable certainty that no harm to any population subgroup, including infants and children, will result from aggregate exposure to this chemical when used as an inert ingredient in pesticide products when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, the exemption from the requirement of a tolerance for residues of PETAE (CAS Reg. No. 68308-48-5), when used as inert ingredient in pre-harvest applications, under 40 CFR 180.920 at a maximum of 20% in pesticide formulations can be considered safe under section 408(q) of the FFDCA.

I. Use Information

Phosphate Ester, Tallow amine, ethoxylated, also known as PETAE, is an industrial chemical. Historically, PETAE has been used to make consumer products such as soaps, cleaning compound and toiletries preparation manufacturing which includes the manufacture of perfumes, shaving and hair preparations, face creams and lotions including sunscreens lotions [Environmental Canada 2007).

II. Substance Identity

PETAE is a UVCB (Unknown or Variable Composition, Complex Reaction Products, or Biological Materials); that is, it is not a discrete chemical and thus may be characterized by a variety of structures. To assist with modeling and further assessments, the structure and corresponding SMILES presented here were chosen to represent the substance.

Table 1. Substance identity for PETAE

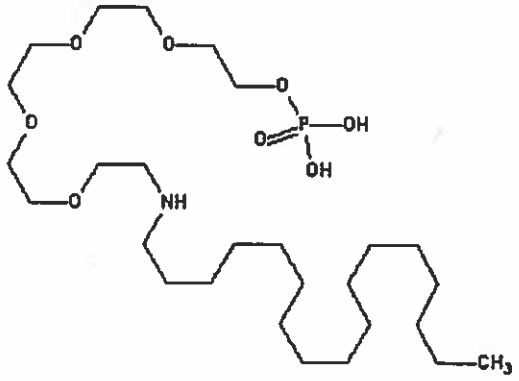
Chemical Abstracts Service Registry Number (CAS RN)	68308-48-5
National Chemical Inventories (NCI) name[1]	Amines, tallow alkyl, ethoxylated, phosphates (TSCA, AICS, ECL, PICCS, ASIA-PAC, NZIoC)
Other names	Tallow amine, ethoxylated, phosphated; Tallowamine, ethoxylated, phosphate salt; Phosphates (chemical category); Polyoxyalkylenes (chemical category); Tallow (chemical category);
Chemical group	Unknown or Variable Composition, Complex Reaction Product, or Biological Material (UVCB)
Major chemical class or use	Surfactant
Major chemical sub-class	Alkyl phosphate ester
Chemical formula	$C_{28}H_{60}N_1O_8P$
Representative chemical structure used to run the estimation model [2]	

Table 1. Substance identity for PETAE	
Representative Simplified Molecular Input Line Entry System (SMILES) used to run the estimation model [2]	CCCCCCCCCCCCCCCCCCNCCOCCOCCOCCOCCOP(=O)(O)O
Molecular mass	569.77 g/mol

[1] National Chemical Inventories (NCI). 2006: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); PICCS (Philippine Inventory of Chemicals and Chemical Substances); NZIoC (New Zealand Inventory of Chemicals); and TSCA (Toxic Substances Control Act Chemical Substance Inventory).
[2] This substance is a UVCB (Unknown or Variable Composition, Complex Reaction Products, or Biological Materials); i.e., it is not a discrete chemical and thus may be characterized by a variety of structures. To assist with modeling, the structure and corresponding SMILES presented here were chosen to represent the substance.

III. Physical and Chemical Properties

No experimental data are available for PETAE.

Table 2 contains modeled (see on Table 1. for the representative chemical structure used to run the estimation model on) physical and chemical properties of PETAE that are relevant to its environmental fate.

Table 2. Estimated Physical Chemical Properties for PETAE (CAS Reg. No. 68308-48-5)		
Parameter	Value	Source
Melting point	90.27°C	EPISuite, 2009
Boiling point	480°C	
Vapor pressure	6.06×10^{-11} mmHg @25°C	
Henry's Law constant	3.96×10^{-21} atm-m^3/mole @25°C	
Octanol/water partition coefficient	Log K_{OW} = 5.53	

Table 2. Estimated Physical Chemical Properties for PETAE (CAS Reg. No. 68308-48-5)

Parameter	Value	Source
Water solubility	0.06006 mg/L at 25°C	EPISuite, 2009
Organic carbon/water partition coefficient	Log K_{oc} = 4.609	
Atmospheric Oxidation	0.052 days (12-hr day; at 25°C	

IV. Human Health Assessment

A. Toxicological Discussion

The Agency has reviewed the data submitted by the petitioner, Huntsman Corporation. Acute and reproductive and developmental toxicity studies are available for PETAE. Studies for repeated dosage toxicity, mutagenicity, and metabolism have not been performed on the subject compound. The toxicological database for PETAE (CAS Reg. 68308-48-5) is limited; however, the Agency has determined that studies on AAPs can be used to assess the toxicity of the PETAE because PETAE is a phosphate ester form of alky amine polyalkoxylates (AAPs).

B. Toxicological Data

The Agency has determined that the available toxicity data are appropriate and adequate to characterize the toxicity of PETAE. Excerpts and summaries of these data are discussed below.

Acute toxicity

The acute toxicity study results for PETAE indicate moderately acute toxicity by oral and low toxicity via dermal and inhalation exposure routes. The chemical is extremely irritating to the eyes, slightly irritating to the skin and not a dermal sensitizer.

Table 3. Summary of Acute Toxicity Data for PETAE		
Parameter	Toxicity Value EPA Toxicity Category	Reference
Oral LD_{50} (rat)	550 mg/kg Category III	MRID No. 47600701
Inhalation LC_{50} Rat (4-hour)	>2.61 mg/L Category IV	MRID No. 47600703
Dermal LD_{50} (rat)	>5050 mg/mg Category IV	MRID No. 47600702
Eye irritation (rabbit)	Extremely Irritating Category I	MRID No. 47600704
Skin irritation (rabbit)	Slightly irritant (PII = 1.0) Category IV	MRID No. 47600705
Skin Sensitization (Guinea Pigs)	Negative for sensitizer	MRID No. 47600706

In an acute oral LD_{50} study in Sprague-Dawley rats, no mortality or clinical signs of toxicity were observed. No clinical sign of toxicity was observed in surviving rats at higher doses. Clinical signs in animals that died included activity decrease, diarrhea, gasping, piloerection and ptosis. The LD_{50} value for Surfactant 8184-92 was 550 mg/kg (MRID 47600701).

In an acute dermal LD_{50} study in Sprague-Dawley rats, there were no effects on clinical signs, body weights or gross necropsy findings at a dose level of 5050 mg/kg. Erythema (dermal irritation) was observed only on Day 1 of the treatment. The dermal LD_{50} value for surfactant 8184-92 was >5050 mg/kg (MRID 47600702).

In an acute inhalation LC_{50} study in Sprague-Dawley rats via nose only method, there were no effects on body weights, mortality or gross necropsy findings at aerosol concentration of 2.61 mg/L. Clinical signs such as decreased activity and pilorection were observed for the first three days. The Mean Median Aerodynamic Diameter (MMAD) was acceptable with average MMAD of 1.8 µm. The inhalation LC_{50} value for the surfactant 8184-92 was > 2.6 mg/L (MRID 47600703).

In a primary skin irritation study in New Zealand white rabbits, the intact test site was treated with 0.5 ml of undiluted test substance and covered with a semi-permeable dressing. The test substance was maintained in contact with the skin for 4 hours. Dermal irritation was scored at 1, 24, and 72 hours, and 7, 10 and 14 days after removal of the dressings. Very slight to well-defined erythema was present at each observation through out the study duration. Edema was not observed. Based on the results of this study, the surfactant 8184-92 is considered as slightly irritating to the rabbit's skin (MRID 47600105).

In a primary eye irritation study in New Zealand White rabbits, undiluted 0.1 ml of the test substance was placed into the conjuctival sac of the right eye of each rabbit. The untreated eye served as the control. All treated eyes were washed with deionized water immediately after 24 hours observation. The treated eyes were scored for irritation at 1 hour and 1 , 2, 3, 7, 10, 14, 17 and 21 days post –instillation. Sever opacity was observed on day 3 and day 4 observation point. Iritis was persisted up to day 17. Redness and chemosis was also observed through out the study. Based on the results of this study, it is concluded that the surfactant 8184-92 is extremely irritating to rabbit's eye (MRID 47600704).

A skin sensitization study was conducted on 15 male and 15 female short-haired albino guinea pigs to determine if test substance Surfactant 8184-92 produced a sensitizing reaction using a modified Buehler method. Males and females were assigned to each of two groups, designated Groups 1(5/sex) and II (10/sex). Group I animals remained untreated during the induction phase of the study and served as a naive control group. Group H animals, the test group, were treated with 0.4 mL of a 75% v/v solution of test substance in corn oil (selected from previous screening), and reduced to a 50% v/v solution of test substance in corn oil. The animals were treated once weekly for three weeks, for a total of three treatments. After a two week rest period, all animals (Groups I and II) were challenged at a virgin test site with an application of 0.4 mL of a 75% v/v solution of test substance in corn oil. The surfactant 8184-92 produced no irritation in the test animals after the challenge treatment, and therefore did not elicit a sensitizing reaction in guinea pigs (MRID 47600706).

Subchronic toxicity

No subchronic studies are available in the database.

Chronic toxicity and carcinogenicity

No chronic toxicity or carcinogenicity data has been found in the scientific literature for PETAE. However, there is no evidence that the AAPs are carcinogenic. EPA has considerable information on the general toxicity of surfactants. These compounds are

shown to cause local irritation and corrosive effects on membrane. EPA recently assessed the toxicity of Alkl Amine Polyalkoxylates (AAPs). PETAE is a phosphate ester form of alkyl amine polyalkoxylates (AAPs). The database on AAPs indicates that the effects do not increase in severity over time (4 weeks to 13 weeks). Based on the lack of progression of severity of effects with time along with the considerable similarities of effects across the species tested and the observation that the vast majority of the effects observed were related to local irritation and corrosive effects, EPA concludes that chronic data are unlikely to show significant differences from existing studies. In addition, the concern for chronic effects for PETAE is low based on SAR, DEREK11 analysis and available data on AAPs.

Neurotoxicity

No effect on Functional Observational Battery (FOB) parameters was observed in the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (MRID 47600707). No clinical sign of neurotoxicity was observed in acute studies.

Mutagenicity / Genetic toxicity

No mutagenicity studies are available on PETAE; however, there was no evidence that the AAPs are mutagenic, or clastogenic.

Developmental and Reproductive Toxicity

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (MRID 47600707), Experimental Surfactant 8184-92 (CAS no. 7664-38-2) was administered orally by gavage to 12 Wistar Han rats/sex/dose at dosage levels of 0, 25, 100 or 200 mg/kg bw/day. Males were dosed 2 weeks prior to the mating period as well as during the mating and post-mating periods until 4 weeks of dosing had been completed. Females were dosed 2 weeks prior to mating, during the mating and gestation periods and until postnatal day 4. Additional satellite animals (5 rats/sex/group) of control and high-dose groups were dosed until the parental animals were terminated and kept an additional 14 days for observation of possible reversibility, persistence or delayed occurrence of toxic effects. One day prior to sacrifice, 5 animals/sex/group (except satellite groups) were tested in a functional observational battery (FOB).

Significant systemic toxicity was not observed in parental animals based on the assessment of FOB, hematology and clinical chemistry parameters, organ weights or macroscopic and microscopic pathology.

Significant parental systemic toxicity was evident only at 200 mg/kg/day based on mortalities, clinical signs, decreased food consumption and decreased body weight/body weight gain in both sexes. Two males in the main study died on exposure days 21 and 29; three females in the main study died on gestation days 7, 9 and 13 and one female in the satellite study died on day 25 of exposure. Clinical signs in these animals included abnormal respiratory sounds, dyspnea, piloerection and emaciation in some animals. These clinical signs also occurred in animals that did not die including main study males during treatment period, satellite males during the treatment and recovery periods and main study females during the pre-mating, gestation and lactation periods and satellite females during the treatment period. These signs were considered as indicative of local irritation and not of systemic origin.

Body weight and food consumption were decreased significantly ($p < 0.05$) in main study males administered 200 mg/kg/day during the 4-week dosing period. In the main study, the body weight was 9 to 12 % less and food consumption was 22 to 39% less when compared to controls in the 200 mg/kg/day males. Body weight gain was decreased in satellite males during the treatment period, but not during the recovery period; food consumption for these animals was decreased during the treatment period and during the second week of the recovery period. Satellite males in the 200 mg/kg/day group only gained 4 g during weeks 0-4 while the control males gained 52 g, and these males ate 17-30% less than controls. Body weight and/or body weight gain were decreased significantly ($p < 0.05$) in main study females administered 200 mg/kg/day during the pre-mating, gestation and lactation periods. The decreases ranged from 7 to 87% less than controls. Body weight and body weight gain in satellite females were not significantly different from controls during the treatment and recovery periods. Significant decreases in food consumption were seen in main study 200 mg/kg/day females during the pre-mating (12-34% less than controls) and gestation periods (11-20% less than controls), but not the lactation period. There were slight decreases in food consumption in satellite females during the treatment and recovery periods.

The parental systemic LOAEL for Experimental Surfactant 8184-92 is 200 mg/kg/day based on mortalities, clinical signs, decreased body weight and/or body weight gain and decreased food consumption in male and female rats. The parental systemic NOAEL is 100 mg/kg/day.

The assessment of reproductive parameters revealed decreased numbers of corpora lutea and implantation sites at 200 mg/kg/day. The gestation index was also decreased at this dosage because 2 pregnant females died during gestation. The mean litter size (live born) was decreased at 200 mg/kg/day, however, the live birth and viability indices were not affected by exposure to the test material. Pup birth weights were comparable between dosed and control groups; however, the 4-day body weight gain was decreased at 200 mg/kg/day.

The reproductive/developmental LOAEL for Experimental Surfactant 8184-92 is 200 mg/kg/day based on decreased numbers of corpora lutea and implantation

sites, decreased litter size and body weight gain in pups. The reproductive/developmental NOAEL is 100 mg/kg/day.

C. Metabolism and Pharmacokinetics

No data have been found in the scientific literature describing the metabolism of PETAE and a very little metabolism information is available for AAPs. However, it is possible to predict mammalian metabolism based on studies for alkyl alcohol alkoxylates, which are another class of surfactants. It has been proposed that the primary metabolic pathway involves the excretion of the polyalkoxylate moiety and conversion of the alkyl amine group to a fatty acid that is then converted via oxidative degradation to carbon dioxide and water.

In general, the gastrointestinal absorption of PETAE with relatively short alkoxylate chain lengths is expected to be rapid and extensive, while less absorption is likely for the more extensive PETAE with larger molecular weights.

Dermal Absorption

There are no dermal absorption data on the PETAE. However, data on functionally and structurally similar surfactants suggest that dermal absorption of the PETAE is likely to be low. Based on the lack of data for the PETAE, large molecules, high log P value and the irritant properties of these surfactants, in order to be health protective, a conservative dermal absorption factor of 5% was selected.

D. Toxicity Endpoint Selection and Levels of Concern

A summary of the points of departure selected may be found in Table 3.

An acute dietary end point was not selected because an appropriate endpoint occurring from a single exposure was not identified.

Table 3. Summary of Toxicological Doses and Endpoints for PETAE for Use in Dietary Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all populations)	No appropriate endpoint was identified for acute dietary assessment			

Table 3. Summary of Toxicological Doses and Endpoints for PETAE for Use in Dietary Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All Populations)	NOAEL = 100 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF = 3x	cRfD = 1.0 cPAD= 0.33 mg/kg/day	**OECD 422 Reproduction/Developmental Screen in rats (MRID 47600707)** LOAEL = 200 mg/kg/day, based on mortalities, clinical signs, decreased body weight and/or body weight gain and decreased food consumption in both sexes **CAS 7664-38-2**
Incidental Oral Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 100 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF = 3x	Residential LOC for MOE = 300	**OECD 422 Reproduction/Developmental Screen in rats (MRID 47600707)** LOAEL = 200 mg/kg/day, based on mortalities, clinical signs, decreased body weight and/or body weight gain and decreased food consumption in both sexes **CAS 7664-38-2**
Dermal and inhalation (All Durations	NOAEL = 100 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF = 3x	Residential /Occupational LOC for MOE = 300	**OECD 422 Reproduction/Developmental Screen in rats (MRID 47600707)** LOAEL = 200 mg/kg/day, based on mortalities, clinical signs, decreased body weight and/or body weight gain and decreased food consumption in both sexes **CAS 7664-38-2**
Cancer (oral, dermal, inhalation)	Classification: No animal toxicity data available for an assessment. Based on SAR analysis, AAPs are not expected to be carcinogenic.			

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

E. Special Considerations for Infants and Children

1. *In general* Section 408(b) (2) (c) of FFDCA provides that EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the FQPA safety factor (SF). In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

2. Prenatal and postnatal sensitivity.

In the case of the PETAE, there was no increased susceptibility to the offspring of rats following prenatal and post-natal exposure in the OPPTS Harmonized Guideline

870.3650 reproductive/developmental screening study. Decreased litter sized and body weight gain in pups was observed at 200 mg/kg/day where maternal/paternal toxicity was manifested as mortalities, clinical signs, decreased body weight and /or body weight gain and decreased food consumption in male and female rats at 200 mg/kg/day. There is no concern for residual uncertainties because clear NOAELs were established for parental and off spring toxicities.

3. Conclusion.

EPA has determined that reliable data show the safety of infants and children would be adequately protected if the FQPA safety factor was reduced to 3X. That decision is based on the following findings:

i. . The toxicity data available on the PETAE consists of one OPPTS Harmonized Guideline 870.3650 combined repeated dose toxicity study with the reproduction/development toxicity screening test (rat); acute oral, dermal, inhalation skin irritation and sensitization, and eye toxicity data. The other studies were bridged from AAPs since PETAE is a phosphate ester form of alky amine polyalkoxylates (AAPs) which have recently assessed by the Agency in docket ID number EPA-HQ-OPP-2008-0738. There was no evidence of immunotoxicity in the database. Furthermore, these compounds do not belong to a class of chemicals that would be expected to be immunotoxic and, there was no evidence that the AAPs are mutagenic, or clastogenic.

ii. No quantitative or qualitative increased susceptibility was demonstrated in the offspring in the OPPTS Harmonized Guideline 870.3650 combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats following prenatal and postnatal exposure.

iii. . There are no chronic studies or carcinogenicity studies are available in the database. EPA has considerable information on the general toxicity of surfactants. These compounds are shown to cause local irritation and corrosive effects on membrane. EPA recently assessed the toxicity of Alkl Amine Polyalkoxylates (AAPs). PETAE is a phosphate ester form of alkyl amine polyalkoxylates (AAPs). The database on AAPs indicates that the effects do not increase in severity over time (4 weeks to 13 weeks). Based on the lack of progression of severity of effects with time along with the considerable similarities of effects across the species tested and the observation that the vast majority of the effects observed were related to local irritation and corrosive effects, EPA concludes that chronic data are unlikely to show significant differences from existing studies. In addition, the concern for chronic effects for PETAE is low based on SAR, DEREK11 analysis and available data on AAPs. Based on the above evidence, EPA concluded that the FQPA factor of 3X for the lack chronic studies would adequate and protective.

iv. No effects were observed on Functional Observation Battery (FOB) parameters in the OPPTS Harmonized Guideline 870.3650 reproductive/developmental screening

study. In addition, no evidence of treatment related clinical signs of neurotoxicity were observed in the available toxicological studies. EPA concluded that there is no need for a developmental neurotoxicity study or additional UFs to account for neurotoxicity.

v. There are no residual uncertainties identified in the exposure databases. The food and drinking water assessment is not likely to underestimate exposure to any subpopulation, including those comprised of infants and children. The dietary exposure assessments are considered to be highly conservative as they are based on the use of the highest tolerance level from the surrogate pesticides for every food and 100% crop treated is assumed for all crops. EPA also made conservative (protective) assumptions in the ground and surface water modeling used to assess exposure to PETAE in drinking water. These assessments will not underestimate the exposure and risks posed by PETAE. Based on the above considerations, EPA has reduced the FQPA factor to 3X.

V. Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, AAPs may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

VI. Exposure Assessment

In examining aggregate exposure, the Federal Food, Drug, And Cosmetic Act (FFDCA) section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use

in gardens, lawns, or buildings (residential and other indoor uses). The primary route of exposure to PETAE from its use as an inert ingredient in pesticide products applied to growing crops would most likely be through consumption of food to which pesticide products containing PETAE have been applied, and possibly through drinking water (from runoff). Residential (dermal and inhalation) exposures are also possible from the use of home garden pesticide products containing PETAE as an inert ingredient.

a. Food Residue Profile

No residue data were submitted for the PETAE inert ingredients. In the absence of data, the Agency has developed an approach which uses surrogate information to derive upper bound exposure estimates for the subject inert ingredients. Upper bound exposure estimates are based on the highest tolerance level residues for a given commodity from a list of 57 high use insecticides (22), herbicides (20), and fungicides (15). The 57 pesticides were selected based on an overall ranking scheme that included consideration of the 1999 data for active ingredients use. All herbicides at greater than 5 million lbs/yr and all fungicides and insecticides at greater than 1 million lbs/yr were included as candidate surrogate chemicals.

OPP assumed that the residue level of the inert ingredient would be no higher than the highest tolerance for a given commodity. Implicit in this assumption is that there would be similar rates of degradation between the active and inert ingredient (if any) and that the concentration of inert ingredient in the scenarios leading to these highest of tolerances would be no higher than the concentration of the active ingredient.

To summarize, the Agency believes the assumptions used to estimate dietary exposures lead to a very conservative assessment of dietary risk for the following reasons:

- the highest tolerance level from the surrogate pesticides for every food is used;
- 100% crop treated is assumed for all crops (every food eaten by a person each day has tolerance-level residues);
- many of these high tolerances are based on very short pre-harvest intervals where there is little time for degradation, whereas actual pesticide applications occur throughout the growing season;
- no consideration was given to potential degradation between harvest and consumption (use of tolerance level residues which are typically one to two orders of magnitude higher than actual residues found in monitoring data);
- Residue values were assigned to every commodity in DEEM™ with no consideration given to potential reduction in residues from washing or cooking.
- A conservative default value of 100 ppb for the concentration of an inert

ingredient in all sources of drinking water was used.

Although sufficient information to quantify actual residue levels in food is not available, the compounding of these conservative assumptions will lead to a significant exaggeration of actual exposures. OPP does not believe that this approach underestimates exposure in the absence of residue data. In the case of PETAE, EPA made a specific adjustment to the dietary exposure assessment to account for the use limitations of the amount of PETAE that may be in formulations (no more than 20% by weight in pesticide formulations) and assumed that PETAE is present at the maximum limitation rather than at equal quantities with the active ingredient. This remains a very conservative assumption because surfactants are generally used at levels far below this percentage.

b. Residential (Non-Occupational) Exposure/Risk Characterization

A screening level occupational and residential exposure and risk assessment was completed for products containing PETAE as inert ingredients. A summary of the residential exposure and risk assessment is presented below. Further details of this residential exposure and risk analysis can be found at http://www.regulations.gov in the memorandum entitled JITF Inert Ingredients. Residential and Occupational Exposure Assessment Algorithms and Assumptions Appendix for the Human Health Risk Assessments to Support Proposed Exemption from the Requirement of a Tolerance When Used as Inert Ingredients in Pesticide Formulations" (D364751, 5/7/09, Lloyd/LaMay in docket ID number EPA-HQ-OPP-2008-0710.

i. Residential Handler Exposure

Exposure Scenarios

In this assessment, the Agency selected representative scenarios, based on end-use product application methods and labeled application rates. The residential products are typically formulated as liquids in concentrates or as wettable powders. The PETAE themselves have no pesticidal properties, and are added to pesticide formulations for their adjuvant properties. PETAE generally are not added to any pesticides intended for indoor use (i.e., where the Agency would typically assess products for indoor residential uses). Therefore, RD assumed no indoor uses exist.

For each of the use scenarios, the Agency assessed residential handler (applicator) inhalation and dermal exposure for outdoor scenarios with high exposure potential (i.e., exposure scenarios with high end unit exposure values) to serve as a screening assessment for all potential residential pesticides containing the PETAE inert ingredients.

Mixer/Loader/Applicator High Exposure Outdoor Scenarios:

- Liquid products: Low Pressure Handwand;
- Liquid products: Hose End Sprayer
- Ready to Use (RTU): Trigger Pump Sprayer Applications

For these assessments, the Agency also used assumptions based on the Residential Exposure Assessment Standard Operating Procedures (SOPs) and the unit exposures were taken from the Pesticide Handlers Exposure Database (PHED).

For all residential handler scenarios, risk estimates are not of concern (i.e., MOEs are all greater than 300) for both the route-specific (dermal or inhalation) assessment and for the total MOE (dermal and inhalation combined). A summary of the results are provided below in APPENDIX D.

ii. Residential Post application Exposure

Exposure Scenarios

Residential post application exposures result when bystanders, such as children come in contact with the PETAE in areas where end-use products have recently been applied (e.g., treated lawns or gardens). As noted above, the PETAE are not added to any pesticides intended for indoor use.

Post application High End Outdoor Exposure Scenarios

- Dermal exposure to treated lawns (adults/children)
- Hand-to-Mouth activity for toddlers on treated lawns (children)
- Object-to-Mouth activity for toddlers on treated lawns (children)
- Soil ingestion from treated soil (children)

The exposures from these routes and scenarios were considered individually and were also added together, where appropriate, to determine a total dose for children exposure to treated lawns. Residential post application exposure is assessed on the day of application, typically referred to as Day 0.

Inhalation exposures are not typically calculated for residential post-application scenarios for the formulation types applicable to the PETAE because inhalation exposures generally account for a negligible percentage of the overall body burden for most pesticide chemicals. This is particularly true for chemicals with a low vapor

pressure such as the PETAE.

For these assessments, the Agency also used assumptions based on the Residential Exposure Assessment Standard Operating Procedures (SOPs) and the unit exposures were taken from the Pesticide Handlers Exposure Database (PHED).

All assessed scenario risk estimates are not of concern (i.e., the MOEs for the assessed scenarios are greater than 300) for both the individual exposure scenario assessed and for the aggregate risk estimates.

VII. Aggregate Risk Assessments and Risk Characterization

As previously noted, the PETAE appear to have very limited use in consumer or personal care products. Given the high end dietary exposure and residential exposure screening level assessments used to address exposure and risk from the uses of the PETAE as inert in pesticide products, and given their limited uses and low concentrations in consumer products, RD believes that the consumer care uses are unlikely to significantly impact aggregate risk.

i. Acute Aggregate Risk

Acute aggregate risk includes dietary exposures to food and drinking water. An aggregate risk assessment was not conducted for the PETAE because no endpoint of concern following the acute exposure was identified in the database.

ii. Chronic Aggregate Risk

There are no data provided regarding PETAE residues in food or any other non occupational exposures to PETAE. In the absence of actual residue data for PETAE, the Agency performed a dietary (food and drinking water) exposure assessment for PETAE for the proposed pre-harvest use using worst case assumptions. A chronic reference dose (cRfD) of 0.33 mg/kg/day was based on the NOAEL of 100 mg/kg/day which was utilized from systemic toxicity derived from the reproductive and developmental toxicity study in rats and a safety factor of 300 (10x for interspecies extrapolation , 10x for intraspecies variations, and 3X FQPA factor). The dietary exposure was calculated as a percentage of the cPAD. The chronic dietary estimate for the U.S. Population was 23.2% (children 1-2 yrs were the most highly exposed population with a chronic exposure estimate occupying 75.6% of the cPAD). The complete dietary exposure assessment is included in appendix C.

iii. Short-Term/Intermediate-Term Aggregate Risk

Short-term and intermediate-term aggregate risk assessments for the PETAE combine high end residential short- or intermediate-term exposures with average food and drinking water exposures, and compare this total to a short- or intermediate term PoD. Short- and intermediate-term aggregate risks are summarized in Appendix E. Short- and intermediate-term aggregate risks are not of concern.

VIII. Occupational Exposure/Risk Pathway

Based on examination of product labels which might potentially contain the PETAE as inert ingredients, RD has determined that exposure to handlers can occur in a variety of occupational environments.

The representative occupational scenarios selected by the Agency for assessment were evaluated based on likely maximum application rates for products which may contain the PETAE as inert ingredients for the short-term exposure assessment, and average application rates for products likely to contain the PETAE as inert for the intermediate- and long-term exposure durations. Active ingredient application rates were corrected for the maximum amount of PETAE likely to be in the final formulations to determine exposure and risk from exposure to the PETAE grouped by fungicide/insecticide or herbicide. A summary of the occupational assessment is presented below.

RD traditionally considers a level of concern (LOC) for these risk assessments to be an MOE of 100 based on the standard 10X inter and 10X intra species extrapolation safety factors.

A. Handler Risk

Exposure Scenarios

Exposure to pesticide handlers is likely during the occupational use of pesticides containing the PETAE as inert ingredient. Dermal and inhalation exposure was estimated using the Pesticide Handlers Exposure Database (PHED) and Outdoor Residential Exposure Task Force (ORETF) data. The quantitative exposure/risk assessment developed for occupational handlers to support the requested exemption for the PETAE is based on the following scenarios. RD notes that these scenarios were

selected to represent the scenarios with the highest potential exposure.

Mixer/Loader/Applicators:

1) Mixer/Loader for aerial application- high acreage field crops (liquids)
2) Mixer/Loader for airblast application- tree nuts crops (both liquid and wettable powder)
3) Mixer/Loader for groundboom application- high acreage field crops and turf (liquids and wettable powder)
4) Applicators for aerial application- high acreage field crops (liquid)
5) Applicators for airblast- tree nut crops
6) Applicators for groundboom- high acreage field crops and turf
7) Mixer/Loader/Applicator- low pressure handwand (liquids and wettable powders)*
8) High pressure handwand- greenhouse (wettable powders)
9) Flagging- high acreage field crops (liquids)

* Uses ORETF unit exposure data. All others use PHED data.

Risk estimates were calculated using the Margin of Exposure (MOE) which is a ratio of the toxicological PoD to the daily dose. Daily dose values are calculated by first calculating exposures by considering application parameters (i.e., rate and area treated) along with unit exposures. Exposures are then normalized by body weight to calculate dose levels. Dermal and inhalation short-and intermediate-term exposure is compared to the dermal and inhalation PoD of 100 mg/kg/day. For both short- and intermediate-term dermal assessments, exposures were adjusted for 5% dermal absorption for comparison to the POD from an oral toxicity study, and inhalation toxicity was assumed to be equivalent to oral toxicity. A combined dermal and inhalation MOE was also calculated for each exposure duration for the PETAE since common toxicity endpoints were identified for both the dermal and inhalation routes of exposure. To assess handler risks, the Agency used surrogate unit exposure data from the Pesticide Handlers Exposure Database (PHED), and ORETF data.

B. Occupational Post application Risk

RD uses the term postapplication to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Postapplication exposure levels

vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for postapplication exposure.

Inhalation exposures are not typically calculated for occupational post-application scenarios because inhalation exposures generally account for a negligible percentage of the overall body burden for most pesticide chemicals.

Exposure Scenarios

This assessment is considered to be a screening level estimate, demonstrating that there are minimal potential risks to workers re-entering fields treated with pesticides containing the PETAE as inert ingredients. While the PETAE are present in formulations designated for crops besides those assessed in this document, risk estimates for those occupational postapplication scenarios are expected to be less than those scenarios assessed in this document (i.e., calculated MOEs will be higher). The three occupational postapplication scenarios assessed are for postapplication activities associated with:

- Tall field/row crops (including scouting, weeding, hand harvesting sweet corn)
- Turf (golf course/sod farm) (including mowing, transplanting, hand weeding)
- Vine/Trellis crops (including scouting, training, tying, thinning, and grape girding and cane turning)

Risks were calculated using the Margin of Exposure (MOE) approach, which is a ratio of the exposure to the toxicological PoD.

A variety of pesticide formulations contain AAPs. PPE is usually not required for worker re-entry, and therefore these postapplication risk estimates are based on the baseline exposure scenario (i.e., typical work clothing but no gloves). Typically, HED characterizes the risk estimate in relation to the restricted entry interval (REI) for a particular active ingredient. While REIs for specific products are not discussed in this risk assessment, occupational post-application scenarios assessed generally result in MOEs that do not indicate risks of concern on Day 0 (the day of application) except for two postapplication scenarios.

Occupational postapplication risk estimates are presented in Appendix F. The risk estimates for the three exposure scenarios assessed resulted in MOEs do not demonstrate risks of concern (i.e., MOEs > 300) on Day 0, except for one scenario:

The short-term worker postapplication activities involving herbicides on corn, specifically the hand-harvesting harvesting/ detassling scenario. That scenario resulted in an MOE of 180 on the day of application (Day 0). Assuming an herbicide application at the

maximum application rate, the MOE would exceed 300 for this scenario at day 13 after application. The Agency notes that it is not expected to be typical agricultural practice to apply herbicides on the same day workers would be conducting hand harvesting and detassling activities. As noted earlier in this assessment, herbicides and insecticides are typically applied relatively early in a growing season. All other postapplication scenarios result in MOEs that do not demonstrate risks of concern on the day of application (Day 0).

IX. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to PETAE and any other substances, and PETAE does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that PETAE has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://ww.epa.gov/pesticides/cumulative/.

X. Environmental Fate Characterization and Drinking Water Considerations

Based on PETAE's estimated physical and chemical properties (Table 2), it is insoluble in water and is expected to predominantly reside in soil or sediment. PETAE is expected to have very high adsorptivity to soil (i.e., expected to be immobile) based upon an estimated log K_{oc} of 4.609. Volatilization from moist soil surfaces seems to be an unimportant fate process based upon an estimated Henry's Law constant. This chemical is not expected to volatilize from dry soil surfaces based upon its vapor pressure. Volatilization from water surfaces is expected to be an unimportant fate process based upon this compound's estimated Henry's Law constant of 7.476×10^{-5} Pa m^3/mol. Thus, if water is a receiving medium, PETAE is expected to partition mainly to sediments and

to a much lesser extent to water [EPI Suite, 2009]. The estimated chemical fate properties of PETAE are given in Appendix A.

XI. Ecotoxicity and Ecological Risk Characterization

There are no available aquatic toxicity studies on PETAE. Given that the substance PETAE is of variable composition, a representative structure was identified and used to estimate physical-chemical properties as well as persistence, bioaccumulation and toxicity and in subsequent modeling in the assessment. There are uncertainties associated with structure chosen, and the properties of the substance estimated using QSAR Models, which were whenever, based on the estimates of toxicity using physical and chemical property. Regarding ecotoxicity, based on the predicted partitioning behavior of this chemical the water column may not be the medium of primary concern.

XII. Analytical Methodology

Since this request is for an exemption from the requirement of a tolerance, an analytical method for enforcement purposes is not required to support this action.

XIII. Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

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APPENDIX A
Physical/Chemical Properties of PETAE

CAS Number: 68308-48-5
SMILES: CCCCCCCCCCCCCCCCCCNCCOCCOCCOCCOCCOP(=O)(O)O
CHEM : Amines, tallow alkyl, ethoxylated, phosphates
MOL FOR: C27 H58 N1 O8 P1
MOL WT: 555.74
---------- EPI SUMMARY (v4.00) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C): ------
Melting Point (deg C): ------
Vapor Pressure (mm Hg): ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole): ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.67 estimate) = 5.53

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 480.00 (Adapted Stein & Brown method)
Melting Pt (deg C): 90.27 (Mean or Weighted MP)
VP (mm Hg, 25 deg C): 6.06E-011 (Modified Grain method)
VP (Pa, 25 deg C): 8.07E-009 (Modified Grain method)
Subcooled liquid VP: 2.58E-010 mm Hg (25 deg C, Mod-Grain method)
: 3.44E-008 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.41):
Water Solubility at 25 deg C (mg/L): 0.06006
log Kow used: 5.53 (estimated)
No-melting pt equation used

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est.) = 3.7116 mg/L

ECOSAR Class Program (ECOSAR v1.00):
Class(es) found:
Aliphatic Amines

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method: 3.96E-021 atm-m3/mole (4.01E-016 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:

HLC: 7.378E-010 atm-m3/mole (7.476E-005 Pa-m3/mole)
VP: 6.06E-011 mm Hg (source: MPBPVP)
WS: 0.0601 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 5.53 (KowWin est)
Log Kaw used: -18.791 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 24.321
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : -0.6442
Biowin2 (Non-Linear Model) : 0.0000
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.2592 (weeks-months)
Biowin4 (Primary Survey Model) : 3.3193 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.3832
Biowin6 (MITI Non-Linear Model): 0.0454
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.2628
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 3.44E-008 Pa (2.58E-010 mm Hg)
Log Koa (Koawin est): 24.321
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 87.2
Octanol/air (Koa) model: 5.14E+011
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1
Mackay model : 1
Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 205.0778 E-12 cm3/molecule-sec
Half-Life = 0.052 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 0.626 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1 (Junge-Pankow, Mackay avg)

1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 4.065E+004 L/kg (MCI method)
Log Koc: 4.609 (MCI method)
Koc : 4800 L/kg (Kow method)
Log Koc: 3.681 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.00):
Log BCF from regression-based method = 1.943 (BCF = 87.67 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.0065 days (HL = 1.015 days)
Log BCF Arnot-Gobas method (upper trophic) = 2.597 (BCF = 395.6)
Log BAF Arnot-Gobas method (upper trophic) = 2.605 (BAF = 403)
log Kow used: 5.53 (estimated)

Volatilization from Water:
Henry LC: 3.96E-021 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 3.485E+017 hours (1.452E+016 days)
Half-Life from Model Lake : 3.802E+018 hours (1.584E+017 days)

Removal in Wastewater Treatment:
Total removal: 88.65 percent
Total biodegradation: 0.75 percent
Total sludge adsorption: 87.90 percent
Total to Air: 0.00 percent
(Using 10000 hr Bio P, A, S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (Kg/hr)
Air	8.12e-011	1.25	1000
Water	8.18	900	1000
Soil	73.5	1.8e+003	1000
Sediment	18.4	8.1e+003	0

Persistence Time: 2.24e+003 hr

APPENDIX B
Ecotoxicity of PETAE

SMILES: CCCCCCCCCCCCCCCCCCNCCOCCOCCOCCOCCOP (=O) (O) O
CHEM : Amines, tallow alkyl, ethoxylated, phosphates
CAS Num: 68308-48-5
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C27 H58 N1 O8 P1
MOL WT : 555.74
Log Kow: 5.53 (KowWin estimate)
Melt Pt:
Wat Sol: 0.06006 mg/L (WskowWin estimate)

ECOSAR v1.00a Class(es) Found

Aliphatic Amines

STRUCTURAL ALERT: THE CHEMICAL YOU ARE ASSESSING SHOULD BE CONSIDERED
FOR EVALUATION AS A:
-----> Surfactants-Anionic
UNDER Special_Classes - Surfactants (Menu Bar, Data entry screen)

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Aliphatic Amines	: Fish	96-hr	LC50	0.732 *
Aliphatic Amines	: Daphnid	8-hr	LC50	0.153 *
Aliphatic Amines	: Green Algae	6-hr	EC50	0.207 *
Aliphatic Amines	: Fish		ChV	0.017
Aliphatic Amines	: Daphnid		ChV	0.030
Aliphatic Amines	: Green Algae		ChV	0.032
Aliphatic Amines	: Fish (SW)	96-hr	LC50	0.806 *
Aliphatic Amines	: Mysid Shrimp (SW)	96-hr	LC50	0.134 *
Aliphatic Amines	: Green Algae (SW)	96-hr	EC50	0.200 *
Aliphatic Amines	: Fish (SW)		ChV	0.017
Aliphatic Amines	: Mysid Shrimp (SW)		ChV	0.030
Aliphatic Amines	: Green Algae (SW)		ChV	0.034
Neutral Organic SAR (Baseline Toxicity)	: Fish	96-hr	LC50	0.439 *
	: Daphnid	48-hr	LC50	0.388 *

: Green Algae	96-hr	EC50	0.713 *
: Fish		ChV	0.039
: Daphnid		ChV	0.067 *
: Green Algae		ChV	0.492 *

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Aliphatic Amines:

For Fish 96-hr LC50: For aliphatic amines with log Kow greater than 7.0, a test duration of greater than 96 hrs may be required for proper expression of toxicity. Also, if the toxicity value obtained by the use of this equation exceeds the water solubility (measured or estimated), mortalities greater than 50% would not be expected in a saturated solution during an exposure period of 96 hrs.

For Daphnid 48-hr LC50: For aliphatic amines with log Kow greater than 5.0, test duration of greater than 48 hrs may be required for proper expression of toxicity. Also, if the toxicity value obtained by the use of this equation exceeds the water solubility (measured or estimated), significant mortalities would not be expected in a saturated solution during an exposure period of 48 hrs.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 7, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Mysid Shrimp Acute Toxicity Values: If the log Kow of the chemical is greater than 6, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Fish and Daphnid Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Green Algae Chronic Toxicity Values: If the log Kow of the chemical is greater than 7.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 6.0 (Fish, Mysid LC50)
Maximum LogKow: 5.0 (Daphnid LC50)
Maximum LogKow: 7.0 (Green Algae EC50)
Maximum LogKow: 8.0 (Fish, Daphnid ChV)

Maximum LogKow: 7.0 (Green Algae ChV)
Maximum Mol Wt: 1000

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

APPENDIX C
DEEM-FCID Chronic analysis for PETAE

U.S. Environmental Protection Agency Ver. 2.00
DEEM-FCID Chronic analysis for PETAE (1994-98 data)
Residue file name: C:\Documents and Settings\adebesai\My Documents\DEEM for PETAE 8-13-09.R98
Adjustment factor #2 used.
Analysis Date 09-28-2009/15:38:20 Residue file dated: 08-13-2009/16:44:35/8
Population adjusted dose (PAD, chronic) = 0.33 mg/kg bw/day
Reference dose (RfD, Chronic) = 1.0 mg/kg bw/day
NOEL (Chronic) = 100 mg/kg bw/day
COMMENT 1: Inert 57 active ingredients + drinking water (100ppb), 20% of PETAE in a formulation

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Margin of Exposure 1/	Percent of cPAD
U.S. Population (total)	**0.076603**	**1,305**	**23.2%**
U.S. Population (spring season)	0.078205	1,279	23.7%
U.S. Population (summer season)	0.077493	1,290	23.5%
U.S. Population (autumn season)	0.075258	1,329	22.8%
U.S. Population (winter season)	0.075496	1,325	22.9%
Northeast region	0.083299	1,200	25.2%
Midwest region	0.076184	1,313	23.1%
Southern region	0.068591	1,458	20.8%
Western region	0.083765	1,194	25.4%
Hispanics	0.080679	1,239	24.4%
Non-hispanic whites	0.075089	1,332	22.8%
Non-hispanic blacks	0.074115	1,349	22.5%
Non-hisp/non-white/non-black	0.098787	1,012	29.9%
All infants (< 1 year)	0.158833	630	48.1%
Nursing infants	0.085084	1,175	25.8%
Non-nursing infants	0.186831	535	56.6%
Children 1-6 yrs	0.198334	504	60.1%
Children 7-12 yrs	0.095936	1,042	29.1%
Females 13-19 (not preg or nursing)	0.055576	1,799	16.8%
Females 20+ (not preg or nursing)	0.059717	1,675	18.1%
Females 13-50 yrs	0.061809	1,618	18.7%
Females 13+ (preg/not nursing)	0.065537	1,526	19.9%
Females 13+ (nursing)	0.077037	1,298	23.3%
Males 13-19 yrs	0.059278	1,687	18.0%
Males 20+ yrs	0.057657	1,734	17.5%
Seniors 55+	0.060972	1,640	18.5%
Children 1-2 yrs	**0.249602**	**401**	**75.6%**
Children 3-5 yrs	0.184783	541	56.0%
Children 6-12 yrs	0.102124	979	30.9%
Youth 13-19 yrs	0.057649	1,735	17.5%
Adults 20-49 yrs	0.057760	1,731	17.5%
Adults 50+ yrs	0.060830	1,644	18.4%
Females 13-49 yrs	0.058156	1,720	17.6%

Appendix D. Short- and Intermediate-Term Exposure and Risks for Residential Handlers of PETAE

Exposure Scenario (Formulation/ Application)	Application Rate[1] (lb inert/ day)	Area Treated Daily[2] (units)	Dermal Unit Exposure (mg/lb inert)[3]	Inhalation Unit Exposure (mg/ lb inert)[3]	Dermal Dose (mg/kg /day)[4]	Inhalation Dose (mg/kg/ day)[5]	Baseline Dermal MOE[6]	Baseline Inhalation MOE[7]	Total MOE[8]
Herbicide Mixer/Loader/Applicator Scenarios									
Liquids/ Low Pressure Handwand	1.125	1	38	0.003	0.03054	4.82×10^{-5}	3,260	2,064,600	3,260
Liquids/ Hose End Sprayer[9]	1.125		11	0.017	0.00884	0.000273	11,320	366,300	10,560
Liquids/ Trigger Sprayer/ Home Garden	1.125		54	0.0019	0.0434	3.05×10^{-5}	2,330	3,263,400	2330
Insecticide and Fungicide Mixer/Loader/Applicator Scenarios									
Liquids/ Low Pressure Handwand	0.45	1	38	0.003	0.0122	1.93×10^{-5}	7,990	5,194,800	7,990
Liquids/ Hose End Sprayer[9]	0.45		11	0.017	0.0035	1.09×10^{-4}	27,970	932,400	27,310
Liquids/ Trigger Sprayer/ Home Garden	0.45		54	0.0019	0.017	1.22×10^{-5}	5,728	7,992,000	57,280

[1]Application rates are based on high end application rates of products containing inerts in the AAPs multiplied by 25% to convert to application rate of just inert in an herbicides product (Herbicide products contain maximum of 25% inert from the AAPs according to Inerts Task Force). For insecticide and fungicide application rates, the AAPs multiplied by 10% to convert to application rate of just inert in an insecticide/fungicide products. Application rates for Short-Term exposure risk estimates are based on maximum product application rates. Application rates for Intermediate-Term exposure risk estimates are based on average product application rates.

[2]Area treated daily values are back-calculated from 5 gallons of product used per day (Revised Residential SOPs 2001).

[3]Unit Exposure values are reported in PHED Surrogate Exposure Guide dated August 1998 except for liquids hose end sprayer scenario (See footnote 9). All exposure scenarios assess exposure reflecting applicators wearing short-sleeved shirts and shorts and no respiratory protection.

[4]Daily Dermal Dose = (Dermal Unit Exposure (mg inert /lb inert) * Application Rate (lb inert /A) * Area Treated (A /day))/ Body Weight (70 kg) * Dermal Absorption Factor of 5% (0.05)

[5] Daily Inhalation Dose = (Inhalation Unit Exposure (µg inert / lb inert) * Conversion Factor (1 mg /1000 µg) * Application Rate (lb inert /A) * Area Treated (A /day)) / Body Weight (70 kg)

[6] Dermal MOE = PoD (NOAEL of 100 mg/kg/day)/ Daily dermal dose (mg/kg/day)

Appendix E. Short- and Intermediate-Term Aggregate Risk Calculations for PETAE						
	Short- and Intermediate-Term					
Population	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food & Water Exposure mg/kg/day	Residential Exposure[3] mg/kg/day	Aggregate MOE (food and residential)[4]
Adult Male ST/IT	100	300	0.3	0.076603	0.056430	752
Adult Female ST/IT	100	300	0.3	0.076603	0.056430	752
Child - ST	100	300	0.3	0.24962	0.0388	347
Child - IT	100	300	0.3	0.249602	0.0190	370

[1] The LOC (Level of Concern) is based on the standard inter- and intra-species uncertainty factors totaling 300.
[2] Maximum Allowable Exposure (mg/kg/day) = PoD/LOC
[3] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. Adult residential exposure combines high end dermal and inhalation handler exposure (Appendix D) with high end post application dermal exposure (Appendix G). Children's residential exposure combines turf dermal exposure with HTM exposures (Appendix G).
[4] Aggregate MOE = [PoD/ (Avg Food & Water Exposure + Residential Exposure)]