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

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Abstract

The Cosmetic Ingredient Review Expert Panel assessed the safety of 47 polyethylene glycols (PEGs) cocamine and related ingredients, which are reported to function mostly as surfactants and antistatic agents. The Panel reviewed the relevant data and developed a framework to satisfy previously identified data deficiencies for this group of materials as well as extend the scope of related materials covered by the analysis. The irritation potential of these ingredients is consistent with the surface active properties that are characteristic of surfactants. The Panel concluded that the PEGs cocamine and related ingredients were safe as ingredients in cosmetic formulations in the current practices of use and concentration when formulated to be nonirritating.

Keywords

safety, cosmetics, PEGs cocamine

Introduction

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polyethylene glycols (PEGs) cocamine and related ingredients based on the relevant published scientific literature and unpublished reports.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

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

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PEG-2 stearamine
PEG-5 stearamine
PEG-10 stearamine
PEG-15 stearamine
PEG-50 stearamine
PEG-2 tallow amine
PEG-7 tallow amine
PEG-11 tallow amine
PEG-15 tallow amine
PEG-20 tallow amine
PEG-22 tallow amine
PEG-25 tallow amine
PEG-30 tallow amine

These ingredients include derivatives of the amines of the fatty acids of coconut oil, oleic acid, soy acid, tallow, and hydrogenated tallow, as well as derivatives of lauramine, palmitamine, rapeseedamine, 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] The PEG-22 tallow amine and PEG-30 tallow amine are reported to function as hair conditioning agents.

This safety assessment includes a rereview 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, PEG-3, PEG-5, PEG-10, PEG-15, and PEG-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 nonstandard bacterial mutagenicity test in which PEG-15 cocamine was negative. Repeated-dose toxicity data were available from a single study in which 10% PEG-15 cocamine was applied to the shaved skin of rats 5 days per week for 6 weeks (30 applications), and no signs of systemic toxicity were found. However, no dermal sensitization data were available for these ingredients. Thus, the CIR Panel determined that the additional data needed included:

- Physical and chemical properties, including impurities (especially nitrosamines),
- Genotoxicity in a mammalian test system (if the results are positive, then a dermal carcinogenesis study may be needed),
- 28-Day dermal toxicity using PEG-2 cocamine,
- Dermal sensitization data on PEG-2 cocamine.

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

The CIR Science and Support Committee (SSC) of the Personal Care Products Council (Council) contended that the gaps in genotoxicity and systemic toxicity data can be filled by applying a framework for identifying and evaluating analogs for read-across analyses.[3] The framework is based on the assessment of structure–activity relationships (SARs) and enables the incorporation of information from the literature and predictive computational tools for physicochemical properties, chemical reactivity, metabolism, and toxicity to identify suitable analogs and develop an overall weight-of-evidence safety assessment. The framework is described in detail in the published literature. The CIR SSC submitted 2 reports to the Panel, one in 2011[4] and another in 2012,[5] in which the framework was used to identify and evaluate analogs for a representative set of PEGs cocamine and to read across from the data available for the analogs. The second CIR SSC submission was preceded by Dr Karen Blackburn's presentation at the CIR Panel Workshop in March 2012, in which she explained the framework and illustrated how the framework could be used for read-across assessment of the PEGs cocamine and related ingredients.[6] The application of the framework to the PEGs cocamine ingredients (specifically the derivatives of coconut oil) was published in March 2015.[7]

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

This safety assessment presents data and analyses from multiple sources, including the Council and the CIR SSC, to facilitate assessing the safety of the PEGs cocamine and related ingredients. The information submitted by the Council and the CIR SSC[4,5] included toxicological data from 2 US Environmental Protection Agency (EPA) high-production volume (HPV) chemicals challenge reports[9,10] and 3 unpublished reports cited in one of the HPV reports.[11-13] The 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, PEG-3, PEG-5, PEG-10, PEG-15, and PEG-20 cocamine. In this safety assessment, selected excerpts from the original safety assessment report are presented as *italicized text*. The excerpts are summaries of the information and issues that the Panel considered for the original assessment and help to inform the present assessment as well.

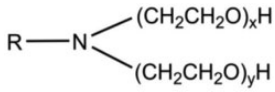
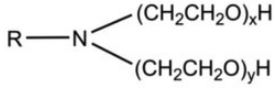
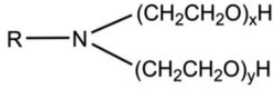
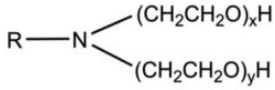
Table 2 lists several previously reviewed ingredients of potential relevance for this assessment and presents the Panel's conclusion and highest reported maximum concentrations for each.

Chemistry

Definition and Structure

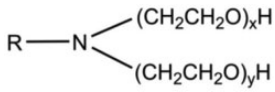
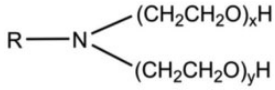
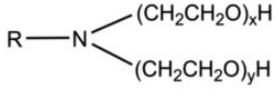
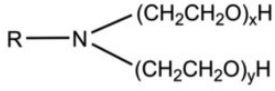
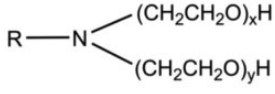
The PEGs cocamine and related ingredients are PEG derivatives of the amines of fatty acids. The chemical structures of these ingredients conform to the following fundamental

Table 1. Definitions and Idealized Structures of the Ingredients in This Safety Assessment.[1]

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

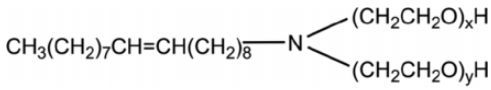
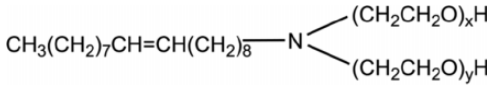
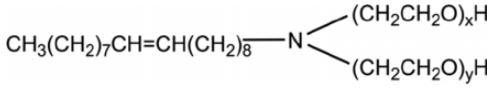
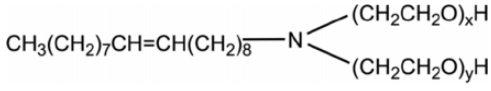
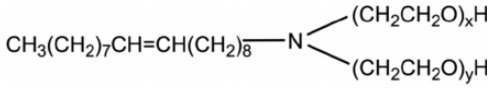
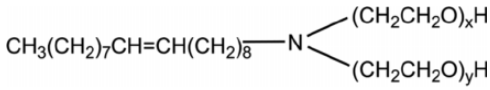
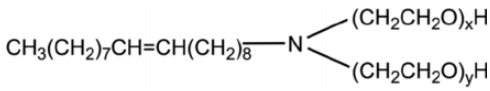
(continued)

Table 1. (continued)

Ingredient CAS no.	Definition/structure	Function
	the group, PEG-2 cocamine, will have 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if $x = 0$ and $y = 2$. The possibility of similar structural variations is notable for PEG-5 cocamine.)[14] (The fatty chains in coconut oil vary from about 8 to 16 carbons long.)[4,45]	
PEG-8 cocamine 61791-14-8 (generic)	PEG-8 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of coconut oil and the $x + y$ of the polyethylene glycol groups has an average value of 8. (The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty acid–derived chain lengths of C12-C14.)[14] (The fatty chains in coconut oil vary from about 8 to 16 carbons long.)[4,45]	Surfactants—Cleansing agents; surfactants—Dispersing agents; surfactants—Emulsifying agents
PEG-10 cocamine 61791-14-8 (generic)	PEG-10 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of coconut oil and the $x + y$ of the polyethylene glycol groups has an average value of 10. (The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty acid–derived chain lengths of C12-C14.)[14] (The fatty chains in coconut oil vary from about 8 to 16 carbons long.)[4,45]	Surfactants—Emulsifying agents
PEG-12 cocamine 61791-14-8 (generic)	PEG-12 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of coconut oil and the $x + y$ of the polyethylene glycol groups has an average value of 12. (The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty acid–derived chain lengths of C12-C14.)[14] (The fatty chains in coconut oil vary from about 8 to 16 carbons long.)[4,45]	Surfactants—Cleansing agents; surfactants—Dispersing agents; surfactants—Emulsifying agents
PEG-15 cocamine 61791-14-8 (generic)	PEG-15 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of coconut oil and the $x + y$ of the polyethylene glycol groups has an average value of 15. (The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty acid–derived chain lengths of C12-C14.)[14] (The fatty chains in coconut oil vary from about 8 to 16 carbons long.)[4,45]	Surfactants—Emulsifying agents
PEG2-20 cocamine 61791-14-8 (generic)	PEG-20 cocamine is a series of polyethylene glycol derivatives of cocamine that conform generally to the formula: 	Surfactants—Emulsifying agents; surfactants—Solubilizing agents

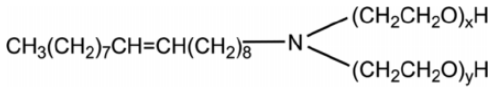
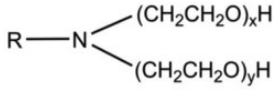
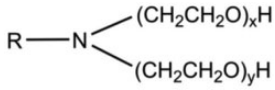
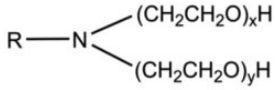
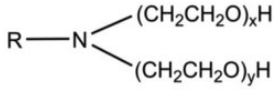
(continued)

Table 1. (continued)

Ingredient CAS no.	Definition/structure	Function
	where R represents the alkyl groups derived from the fatty acids of coconut oil and the x + y of the polyethylene glycol groups has an average value of 20. (The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are described in Table 4. Thus, each PEGs cocamine is a mixture of compounds with the major fatty acid–derived chain lengths of C12-C14.)[14] (The fatty chains in coconut oil vary from about 8 to 16 carbons long.)[4,45]	
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 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x = 0 and y = 2.)[14]	Surfactants—Emulsifying agents; surfactants—Foam boosters
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 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x = 0 and y = 2. The possibility of similar structural variations is notable for PEG-5 oleamine.)[14]	Antistatic agents; surfactants—Emulsifying agents
PEG-6 oleamine 26635-93-8 (generic)	PEG-6 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x + y has an average value of 6.	Surfactants—Emulsifying agents; surfactants—Foam boosters
PEG-10 oleamine 26635-93-8 (generic)	PEG-10 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x + y has an average value of 10.	Not reported
PEG-15 oleamine 26635-93-8 (generic)	PEG-15 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x + y has an average value of 15.	Antistatic agents; surfactants—Emulsifying agents
PEG-20 oleamine 26635-93-8 (generic)	PEG-20 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x + y has an average value of 20.	Not reported
PEG-25 oleamine 26635-93-8 (generic)	PEG-25 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x + y has an average value of 25.	Not reported

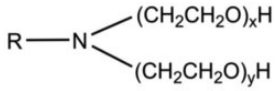
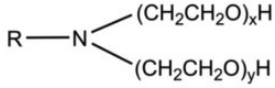
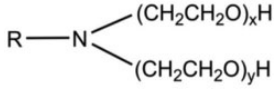
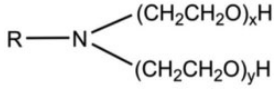
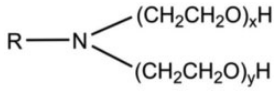
(continued)

Table 1. (continued)

Ingredient CAS no.	Definition/structure	Function
PEG-30 oleamine 26635-93-8 (generic)	PEG-30 oleamine is a series of polyethylene glycol derivatives of oleic acid that conform generally to the formula:  where x + y has an average value of 30.	Antistatic agents; surfactants—Cleansing agents; surfactants—Solubilizing agents
PEG-2 tallow amine 61791-26-2 (generic)	PEG-2 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x + y has an average value of 2. (The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty acid–derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups. The structure of PEG-2 tallow amine will have 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have 1 hydrogen atom and 1 *N*-polyethoxyl group if x = 0 and y = 2.)[14] (The fatty chains in tallow vary from about 14 to 18 carbons long.)[4]	Antistatic agents
PEG-7 tallow amine 61791-26-2 (generic)	PEG-7 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x + y has an average value of 7. (The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty acid–derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups.) (The fatty chains in tallow vary from about 14 to 18 carbons long)[4]	Antistatic agents
PEG-11 tallow amine 61791-26-2 (generic)	PEG-11 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x + y has an average value of 11. (The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty acid–derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups.) (The fatty chains in tallow vary from about 14 to 18 carbons long.)[4]	Antistatic agents
PEG-15 tallow amine 61791-26-2 (generic)	PEG-15 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x + y has an average value of 15. (The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty acid–derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups.) (The fatty chains in tallow vary from about 14 to 18 carbons long.)[4]	Antistatic agents

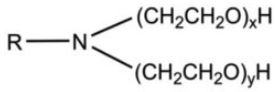
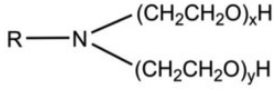
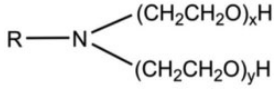
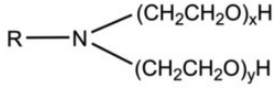
(continued)

Table 1. (continued)

Ingredient CAS no.	Definition/structure	Function
PEG-20 tallow amine 61791-26-2 (generic)	PEG-20 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x + y has an average value of 20. (The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty acid–derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups.) (The fatty chains in tallow vary from about 14 to 18 carbons long.)[4]	Antistatic agents
PEG-22 tallow amine 61791-26-2 (generic)	PEG-22 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x + y has an average value of 22. (The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty acid–derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups.) (The fatty chains in tallow vary from about 14 to 18 carbons long.)[4]	Hair coloring agents
PEG-25 tallow amine 61791-26-2 (generic)	PEG-25 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x + y has an average value of 25. (The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty acid–derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups.) (The fatty chains in tallow vary from about 14 to 18 carbons long.)[4]	Antistatic agents
PEG-30 tallow amine 61791-26-2 (generic)	PEG-30 tallow amine is a series of polyethylene glycol derivatives of tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of tallow and x + y has an average value of 30. (The distribution of chain lengths and degree of unsaturation of the fatty acids in tallow are described in Table 5. Therefore, each PEGs tallow amine is a mixture of compounds with the major fatty acid–derived chain lengths of C16 and C18 with a considerable fraction consisting of unsaturated alkyl groups.) (The fatty chains in tallow vary from about 14 to 18 carbons long.)[4]	Hair coloring agents
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.	Antistatic agents; surfactants—Foam boosters

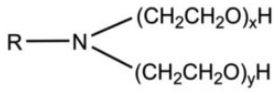
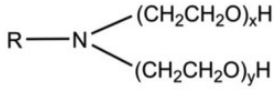
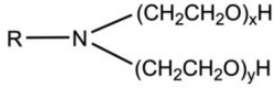
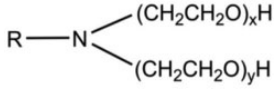
(continued)

Table 1. (continued)

Ingredient CAS no.	Definition/structure	Function
	(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 2 *N*-hydroxyethyl groups, rather than *N* polyethoxyl groups, if x and y both equal 1. The structure will have 1 hydrogen atom and 1 *N*-polyethoxyl group if x = 0 and y = 2. The possibility of similar structural variations is notable for PEG-5 hydrogenated tallow amine. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	
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 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have one hydrogen atom and one *N*-polyethoxyl group if x = 0 and y = 2. The possibility of similar structural variations is notable for PEG-5 hydrogenated tallow amine. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	Antistatic agents
PEG-8 hydrogenated tallow amine 61791-26-2 (generic)	PEG-8 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x + y has an average value of 8. (In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	Antistatic agents, surfactants—Emulsifying agents
PEG-10 hydrogenated tallow amine 61791-26-2 (generic)	PEG-10 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x + y has an average value of 10. (In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	Antistatic agents; surfactants—Emulsifying agents
PEG-15 hydrogenated tallow amine 61791-26-2 (generic)	PEG-15 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula: 	Antistatic agents; surfactants—Emulsifying agents

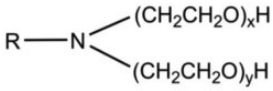
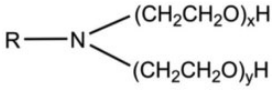
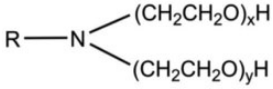
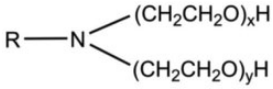
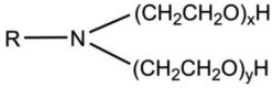
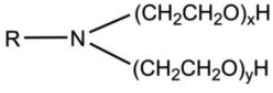
(continued)

Table 1. (continued)

Ingredient CAS no.	Definition/structure	Function
	where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x + y has an average value of 15. (In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	
PEG-20 hydrogenated tallow amine 61791-26-2 (generic)	PEG-20 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x + y has an average value of 20. (In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	Antistatic agents; surfactants—Emulsifying agents; surfactants—Solubilizing agents
PEG-30 hydrogenated tallow amine 61791-26-2 (generic)	PEG-30 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x + y has an average value of 30. (In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	Antistatic agents; surfactants—Solubilizing agents
PEG-40 hydrogenated tallow amine 61791-26-2 (generic)	PEG-40 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x + y has an average value of 40. (In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	Antistatic agents; surfactants—Solubilizing agents
PEG-50 hydrogenated tallow amine 61791-26-2 (generic)	PEG-50 hydrogenated tallow amine is a series of polyethylene glycol derivatives of hydrogenated tallow that conform generally to the formula:  where R represents the alkyl groups derived from the fatty acids of hydrogenated tallow and x + y has an average value of 50. (In hydrogenated tallow, the degree of unsaturation of the fatty acids is reduced or eliminated by hydrogenation. Partial hydrogenation of the tallow used to produce this ingredient may yield PEGs hydrogenated tallow amine with trans-fatty acid moieties.)[14] (The fatty chains in PEGs-2 hydrogenated tallow vary from about 12 to 20 carbons long)[12,13,46]	Antistatic agents; surfactants—Solubilizing agents

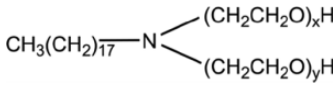
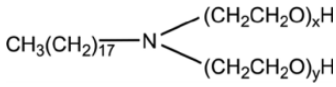
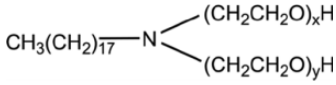
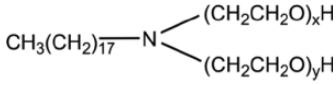
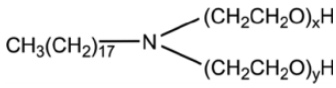
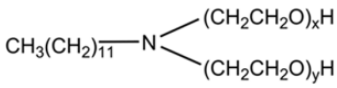
(continued)

Table 1. (continued)

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

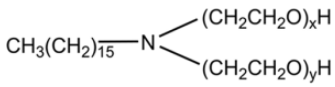
(continued)

Table 1. (continued)

Ingredient CAS no.	Definition/structure	Function
	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 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have 1 hydrogen atom and 1 *N*-polyethoxyl group if x = 0 and y = 2.)[14] (The fatty chains in rapeseed oil are predominantly 16 to 22 carbons long)[15,45]	
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 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have 1 hydrogen atom and 1 *N*-polyethoxyl group if x = 0 and y = 2.)[14]	Antistatic agents; surfactants—Foam boosters
PEG-5 stearamine 9003-93-4 (generic)	PEG-5 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x + y has an average value of 5. (The structure of the smallest member of the group, PEG-2 stearamine, will have 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have 1 hydrogen atom and 1 *N*-polyethoxyl group if x = 0 and y = 2. The possibility of similar structural variations is notable for PEG-5 stearamine.)[14]	Antistatic agents; surfactants—Emulsifying agents
PEG-10 stearamine 9003-93-4 (generic)	PEG-10 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x + y has an average value of 10.	Antistatic agents; surfactants—Emulsifying agents
PEG-15 stearamine 9003-93-4 (generic)	PEG-15 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x + y has an average value of 15.	Antistatic agents; surfactants—Emulsifying agents
PEG-50 stearamine 9003-93-4 (generic)	PEG-50 stearamine is the polyethylene glycol derivative of stearyl amine that conforms to the formula:  where x + y has an average value of 50.	Antistatic agents; surfactants—Solubilizing agents
PEG-2 lauramine no CAS# provided	PEG-2 lauramine is the polyethylene glycol derivative of lauryl amine that conforms to the formula:  where the alkyl group is derived from lauric acid (C12) and x + y has an average value of 2. (The structure of PEG-2 lauramine will have 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, if x and y both equal 1. The structure will have 1 hydrogen atom and 1 *N*-polyethoxyl group if x = 0 and y = 2.)[14]	Antistatic agents; surfactants—Foam boosters

(continued)

Table 1. (continued)

Ingredient CAS no.	Definition/structure	Function
PEG-12 palmitamine 68155-33-9, generic	PEG-12 palmitamine is the polyethylene glycol derivative of palmitamine that conforms to the formula:  where the alkyl group is derived from palmitic acid (Cl6) and x + y of the polyethylene glycol groups has an average value of 12. (The fatty chains in palm oil vary from about 8 to 18 carbons long.)[45]	Antistatic agents; surfactants—Emulsifying agents

Abbreviation: PEG, polyethylene glycols

Table 2. Previously Reviewed Ingredients of Potential Relevance.

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

(continued)

Table 2. (continued)

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

formula (Figure 1), where R represents alkyl groups derived from the fatty acids and the $x + y$ of the PEG groups have average values equal to the number in the International Nomenclature Cosmetic Ingredient (INCI) name (Table 1).[1]

For example, PEG-4 cocamine is the PEG 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 PEG derivative of tallow, where R represents alkyl groups derived from the fatty acids of tallow and $x + y$ has an average value of 7. Thus, each ingredient in this group is a mixture of substances with various lengths of the PEG moieties and various lengths and degrees of unsaturation of the alkyl fatty acid moieties (Table 1).[14]

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

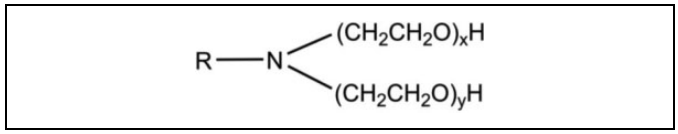


Figure 1. General chemical structure of polyethylene glycols (PEGs) cocamine and related ingredients

In coconut oil, saturated fatty acids with chain lengths of C12 (44%-53%) predominate, and there were smaller fractions of unsaturated C16 (0%-1%) and C18 (6%-12%) chains (Table 4).[4] In tallow, by contrast, unsaturated fatty acids with chain lengths of C18 (39%-59%) predominate, and there were substantial fractions of saturated C16 (20%-37%) and C18 (14%-21%) chains (Table 5).[4] Unsaturated fatty acids with chain lengths of C18 predominate in rapeseed oil (>32%->96%; Table 6) and in soybean oil (>40%->60%; Table 7).[15]

Table 3. Supplier Specifications and Analytical Data for PEGs Cocamine and Related Ingredients.

Property	Value	Reference
PEG-2 cocamine		
Physical appearance at 25°C	Yellow to amber liquid/clear liquid	5/17
Color, Gardner scale	2.0 max./11.0 max.	5/17
Refractive index at 25°C	~1.466	17
pH (10% in IPA/H_2O)	9.0-11.0	5
Amine value	185-200	17
Secondary amine (%)	0.5 max.	19
Primary and secondary amine (%)	5.0 max.	17
Tertiary amine (%)	97.0 min./95.0 max./95 min./97-100	5/17/56/19
Nitrosamine (ppb)	50 max.	19
Moisture (%)	0.5 max./1.0 max./residual	5/17/19
Neutralization equation	290-310/280-303	5/17
PEG-5 cocamine		
Physical appearance	Yellow to amber liquid/liquid at 25°C	57/58
Color (Gardner)	12.0 max./7 max.	57/58
Specific gravity at 25°C	0.976	58
Viscosity (kg/[seconds × meter]) at 20°C	0.15	58
Vapor pressure (mm Hg) at 20°C	<0.1	58
Melting point (°C)	−9	58
Boiling point (initial;°C) at 760 mm Hg	>300	58
pH (5% soln.)	9.0-11.0	57
Amine value	128-138/129-137	57/58
Secondary amine (%)	0.5 max.	19
Primary and secondary amine (%)	2 max.	58
Tertiary amine (%)	96 min./95 min./97-100	57/56/19
Nitrosamine (ppb)	50 max.	19
Moisture (%)	1.0 max./residual/1 max.	57/19/58
Neutralization Equation	406-439/410-435	57/58
PEG-15 cocamine		
Physical appearance	Yellow to amber liquid	5,59
Color (Gardner)	9.0 max./12 max.	5/59
pH (10% in IPA/H_2O/5% soln.)	9.0-11.0/9-10.5	5/59
Amine value	62-68	59
Tertiary amine (%)	96 min.	5,59
Moisture (%)	1.0 max.	5,59
Neutralization equation	825-905	5,59
PEG-2 tallow amine		
Physical appearance	Liquid to semisolid (paste)/pale brown-yellow liquid/Paste at 25°C	60/13,46/61
Color (Gardner)	8 max./6 max.	60/61
Average molecular weight (g/mol)	344/343	13,46/12
Specific gravity at 25°C	0.916	61
Viscosity (kg/[seconds × meter]) at 50°C	0.034	61
Vapor pressure (mm Hg) at 20°C	<0.1	61
Melting point (°C)	29	61
Boiling point (initial;°C) at 760 mm Hg	>300	61
Amine value	156-165	61
Primary amine (%)	0.4/0.8	46/12
Secondary amine (%)	0.7/0.7	46/12
Primary and secondary amine (%)	1.2/1.5/3 max.	13,46/12/61
Tertiary amine (%)	97.0 min./98.6/98.5/96	60/13,46/12/61
Chain length distributions (%)	C12E2: 1.5/0.3 C18E2: 2.2/2.3 C14E2: 3.0/1.6 C18E2: 51.7/54.4 C15E2: 1.0/4.4 C16E3: 1.4/0.9 C16E2: 0.2/0.5 C18E3: 2.2/1.2 C16E2: 34.2/29.9 C20E2: 0.7/2.0 C17E2: 1.9/1.5 Unknown: not reported/1	13,46/12
Moisture (%)	1.0 max.	60
Neutralization Equation	350-370/340-360	60/61

(continued)

Table 3. (continued)

Property	Value	Reference
PEG-5 tallow amine		
Physical appearance	Clear liquid/liquid-paste at 25°C	62/63
Color (Gardner)	8 max./7 max.	62/63
Specific gravity at 25°C	0.950	64
Vapor pressure (mm Hg) at 20°C	<0.1	64
Melting point (°C)	12	64
Boiling point (initial;°C) at 760 mm Hg	>300	64
pH (10% in IPA/H_2O)	9-11/11-11.6	62/63
Solubility (5% at 20°C)	Water, acetone, isopropanol, propylene glycol, xylene, ethanol	64,65
Amine value	113-119	64
Primary and secondary amine (%)	2 max.	64
Tertiary amine (%)	97 min./95 min./98 min.	62/56/63
Moisture (%)	1 max./1 max.	62/63
Neutralization equation	475-495/470-495	62/63
PEG-15 tallow amine		
Physical appearance	Clear liquid/liquid-paste at 25°C	66/67
Color (Gardner)	8 max./8 max.	66/67
Specific gravity at 25°C	1.024	67
Vapor pressure (mm Hg) at 20°C	<0.1	67
Melting point (°C)	−3	67
Boiling point (initial;°C) at 760 mm Hg	>300	67
pH (5% soln.)	9-10.5/11-11.6	66/67
Solubility at 25°C	Water, acetone, isopropanol	67
Amine value	59-63/59-63	66/67
Primary and secondary amine (%)	1 max.	67
Tertiary amine (%)	97 min.	66
Moisture (%)	1.0 max./1 max.	66/67
Neutralization equation	890-951/890-950	66/67
PEG-2 hydrogenated tallow amine		
Physical appearance	Solid at 25°C	68
Color, Hazen	300 max.	68
Solubility at 20°C	Water, ethanol, propylene glycol	68
Density (kg/m^3) at 50°C	880	68
Viscosity (kg/[seconds × meter]) at 50°C	0.042	68
Activity (%)	100	68
Tertiary amine (%)	95 min./ 97 min.	56/68
Moisture (%)	1.0 max.	68
Neutralization equation	338-360	68
PEG-8 hydrogenated tallow amine		
Physical appearance	Amber viscous liquid (200°C)	5
Solubility in water at 20°C	0.4%; dispersion at >0.4%	5
Specific gravity at 200°C	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
PEG-5 oleamine		
Solubility	Water soluble	5
Specific gravity at 25°C	0.94	5
PEG-15 oleamine		
Solubility	Water soluble	5
Specific gravity at 25°C	1.01	5
PEG-5 soyamine		
Physical appearance	Clear liquid at 25°C	69
Color (Gardner)	10 max.	69
Specific gravity at 25°C	0.952	69
Vapor pressure (mm Hg) at 20°C	<1	69
Melting point (°C)	6	69

(continued)

Table 3. (continued)

Property	Value	Reference
Boiling point (initial;°C) at 760 mm Hg	>300	69
Amine value (mg KOH/g)	113-119	69
Primary and secondary amine (%)	3 max.	69
Moisture (%)	1 max.	69
Neutralization Equation	470-495	69
PEG-15 soyamine		
Physical appearance	Clear liquid at 25°C	70
Color (Gardner)	10 max.	70
Specific gravity at 25°C	1.023	70
Melting point (°C)	−8	70
Boiling point (initial;°C) at 760 mm Hg	>300	70
pH	11.5	70
Amine value	59-63	70
Primary and secondary amine (%)	1 max.	70
Moisture (%)	1 max.	70
Neutralization equation	895-955	70
PEG-5 stearamine		
Physical appearance at 25°C	Yellow soft solid/solid at 25°C	71/72
Color, (Gardner scale)	9 max./5 max.	71/72
Specific gravity at 60°C	0.876	72
Viscosity (kg/[seconds × meter]) at 50°C	0.068	72
Vapor pressure (mm Hg) at 25°C	<0.1	72
Melting point (°C)	50	72
Boiling point (initial;°C) at 760 mm Hg	>300	72
pH (5% soln.)	9.0-10.0	71
Hydroxyl number	210-240	71
Amine value	110-120/150-160	71/72
Primary and secondary amine (%)	3 max.	72
Tertiary amine (%)	97 min./95 min./97 min.	71/56/72
Moisture (%)	1.0 max.	71/72
Neutralization equation	470-510	71
PEG-10 stearamine		
Solubility	Water soluble	5
Specific gravity at 25°C	0.98	5
PEG-15 stearamine		
Physical appearance at 25°C	Liquid-paste at 25°C	73
Color (Gardner scale)	8 max.	73
Specific gravity at 50°C	1.015	73
Vapor pressure (mm Hg) at 20°C	<0.1	73
Melting point (°C)	9	73
Boiling point (initial;°C) at 760 mm Hg	>300	73
pH	11-11.6	73
Amine value	58-62	73
Primary and secondary amine (%)	1 max.	73
Moisture (%)	1 max.	73
Neutralization Equation	900-960	73

Abbreviation: PEG, polyethylene glycol

Chemical and Physical Properties

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

Method of Manufacture

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

Table 4. Chain Length Distribution and Degree of Unsaturation of the Fatty Acids in Coconut Oil.[45]

Fatty acids	Fatty acid chain length	Degree of Unsaturation	Composition
Caproic	C6	None	0%-1%
Caprylic	C8	None	5%-9%
Capric	C10	None	5%-10%
Lauric	C12	None	44%-53%
Myristic	C14	None	13%-19%
Palmitic	C16	None	8%-11%
Stearic	C18	None	1%-3%
Palmitoleic	C16	1	0%-1%
Oleic	C18	1	5%-8%
Linoleic	C18	2	1%-3%

Table 5. Chain Length Distribution and Degree of Unsaturation of the Fatty Acids in Tallow.[4]

Fatty acid chain length	Degree of unsaturation	Composition
C14	None	0%-6%
C16	None	20%-37%
C18	None	14%-21%
C16	1	3%-9%
C18	1	35%-46%
C18	2	4%-10%
C18	3	0%-3%

Table 6. Chain Length Distribution and Degree of Unsaturation of the Fatty Acids in Rapeseed Oil.[15,45]

Fatty acids	Fatty acid chain length	Degree of unsaturation	Composition
Palmitic	C16	None	1.5%-4.5%
Stearic	C18	None	0.7%-1.5%
Oleic	C18	1	12.1%-61.7%
Linoleic	C18	2	11.4%-22.1%
Linolenic	C18	3	8.3%-12.5%
Eicosenioc	C20	1	5.6%-10.9%
Erucic	C22	1	0.2%-58.6%

Table 7. Chain Length Distribution and Degree of Unsaturation of the Fatty Acids in Soybean Oil.[15]

Fatty acids	Fatty acid chain length	Degree of unsaturation	Composition
Oleic	C18	1	11.5%-60%
Linoleic	C18	2	25%-63.1%
Linolenic	C18	3	2.9%-12.1%

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

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

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

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

Impurities/Constituents

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

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

The PEGs cocamine and related ingredients, like the PEGs, may contain traces of 1,4-dioxane (which is a by-product of ethoxylation) and ethylene oxide as impurities[2,16,18]; the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and thus uses additional purification steps to limit it in these ingredients before blending into cosmetic formulations. In addition, these ingredients are mixtures of tertiary alkyl amines that may also contain some secondary or primary amines. Thus, the formation of nitrosamines in

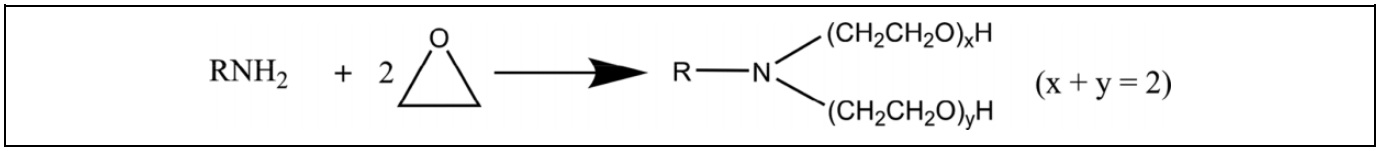


Figure 2. Ethoxylation of fatty amines, step 1.

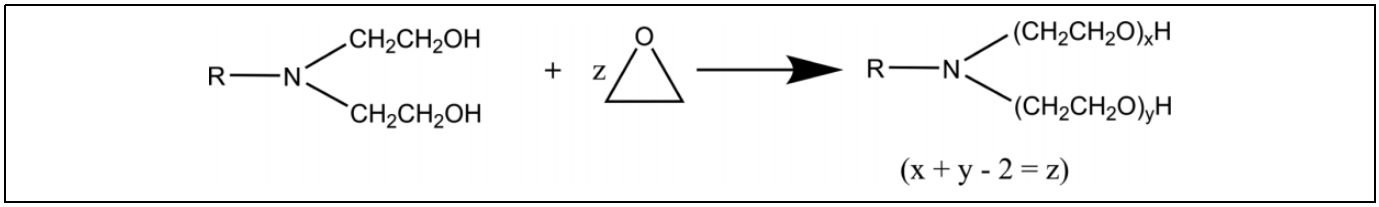


Figure 3. Ethoxylation of fatty amines, step 2.

formulation should be considered. The maximum concentration of nitrosamine was reported by a supplier to be 50 ppb in PEG-2 cocamine (Table 3).[19]

Use

Cosmetic

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

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

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

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

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

Some of the ingredients in use are reported to be used in body and hand sprays and could possibly be inhaled. For example, PEG-15 cocamine was reported to be used in body and hand sprays at a highest maximum concentration of 3%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[22,23] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[24,25]

Noncosmetic

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

Table 8. Frequency (2015) and Concentration of Use (2014) According to Duration and Type of Exposure for PEGs Cocamine Ingredients.[20,21,74]

	# of uses	Max conc of use (%)	# of uses	Max conc of use (%)	# of uses	Max conc of use (%)	# of uses	Max conc of use (%)
	PEG-5 hydrogenated tallow amine		PEG-8 hydrogenated tallow amine		PEG-2 oleamine		PEG-2 rapeseedamine	
Totals[a]	1	NR	4	NR	254	0.1-3.5	255	NR
Duration of use								
Leave-on	NR	NR	NR	NR	NR	0.16	NR	NR
Rinse off	1	NR	4	NR	239	0.1-3.5	255	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental inhalation—powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal contact	NR	NR	NR	NR	NR	0.16	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair—coloring	1	NR	4	NR	254	0.1-3.5	255	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR	NR	NR

	PEG-2 soyamine		PEG-5 soyamine		PEG-2 tallow amine	
Totals[a]	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—noncoloring	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

Abbreviations: NR, not reported; PEG, polyethylene glycol.
[a]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.

hydrogenated tallow amine).[27] The POEA is listed by US EPA as a pesticide inert ingredient.[28]

Toxicokinetics

The PEG cocamine absorption and metabolism data were not available.[2] The PEG absorption is related to whether the substance is a liquid or a solid. The 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 to 1.3 g/kg.[2]

Table 9. Current and Historical Frequency and Concentration of Use of PEGs Cocamine According to Duration and Exposure.[2,20,21,74]

	# of uses		Max conc of use (%)		# of uses		Max conc of use (%)	
	2015	1996	2014	1995	2015	1996	2014	1995
	PEG-2 cocamine				PEG-3 cocamine			
Totals[a]	107	15	0.33	NR[b]	NR	14	NR	NR[b]
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
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	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—noncoloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair—coloring	107	15	NR	NR	NR	14	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR	NR	NR
	2015	1996	2014	1995	2015	1996	2014	1995
	PEG-5 cocamine				PEG-15 cocamine			
Totals[a]	1	NR	NR	NR[b]	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[c]; 2[d]	3; 13[c]; 2[d]	3	1.0; 0.8[c]
Incidental inhalation—powder	NR	NR	NR	NR	2[d]	1; 2[d]	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—noncoloring	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
	2015	1996	2014	1995				
	PEG-20 cocamine							
Totals[a]	NR	38	NR	NR[b]				
Duration of use								
Leave-on	NR	NR	NR	NR				
Rinse off	NR	37	NR	NR				
Diluted for (bath) use	NR	1	NR	NR				
Exposure type								
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				

(continued)

Table 9. (continued)

	# of uses		Max conc of use (%)		# of uses	Max conc of use (%)
	2015	1996	2014	1995		
	PEG-20 cocamine					
Totals[a]	NR	38	NR	NR[b]		
Dermal contact	NR	1	NR	NR		
Deodorant (underarm)	NR	NR	NR	NR		
Hair—noncoloring	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		

Abbreviations: NR, no reported use; PEG, polyethylene glycol.
[a]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.
[b]Unspecified PEGs cocamine ingredient was reported to have a concentration of 8% to 20% in hair coloring products.
[c]It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[d]Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder; therefore, the information is captured in both categories.

Table 10. Ingredients That Are Not Reported to be in Use.

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

Abbreviation: PEG, polyethylene glycol.

Oral

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

Ten Sprague Dawley rats (n = 5/sex/dose) received a single 2 g/kg dose of PEG-2 tallow amine in peanut oil by gavage.[9] The rats were observed for 14 days after exposure. All of the rats exhibited hunched posture and piloerection 1 hour after treatment, but appeared normal 4 hours after treatment. None of the rats died before the scheduled sacrifice. No effects were found on necropsy. The LD_{50} was reported to be >2,000 mg/kg.

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

Groups of 10 albino Sprague Dawley rats (n = 5/sex/dose) received a single 0.16, 0.4, 1, 2.5, or 6.25 g/kg dose of undiluted PEG-20 tallow amine by gavage.[9] The animals were examined for mortality and signs of toxicity 0.5, 1, 2.5, and 4 hours after exposure and then daily throughout the 14-day observation period. None of the rats of the 160 mg/kg group

died during the observation period. Several animals in the 0.16 g/kg group showed mild signs of toxicity (piloerection; ataxia; decreased activity; discharge around the eyes, nose, and mouth; and diarrhea) during the first few days after exposure, but appeared normal within about 4 days. In addition to these signs, the animals of all of the other groups exhibited stained abdomen and anogenitals, emaciation, excess salivation, red crusty material around the nose, and decreased activity. Surviving animals of the 1 g/kg group also exhibited red crusty material on face, soft stools, decreased limb tone, prolapsed penis, and hypothermia. Necropsy revealed a dose-dependent increase in the incidence of lesions associated with irritation, and fluid accumulation in the stomach and lower gastrointestinal tract, as well as evidence of congestion in the lungs and thymus. The LD_{50} was estimated to be 0.63 g/kg of body weight (95% confidence intervals = 0.45-0.89 g/kg).

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

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

Dermal

Polyethylene glycol 20 tallow amine. New Zealand white rabbits (n = 3/sex/dose) received a single 2 mL/kg application of undiluted liquid PEG-20 tallow amine on the clipped skin of the back.[9] The skin was abraded before the application of the test substance in 2 of the male and 1 of the female rabbits. The exposure sites were occluded with gauze bandages, dental dams, and tape for 24 hours after the application. Rabbits were observed twice daily for signs of dermal irritation for 14 days after removing the bandage and excess test substance. One female exhibited signs of respiratory congestion from days 3 through 14 of the observation period, and another female exhibited dehydration from days 10 through 14. Necropsy revealed that the lungs of a male rabbit were dark red with small, multifocal, raised areas. These lesions were considered to be attributable to a latent respiratory infection known to be common in this species and were not considered to be treatment related. One lobe of the liver of a male rabbit exhibited pinpoint-size white foci, and a female had several, small tan areas throughout the liver. The etiology of the liver lesions is unknown. None of the animals died during the observation period, and the reported LD_{50} was >2.0 mL/kg (males and females combined).

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

New Zealand white rabbits (n = 3/sex/dose) received a single 2 mL/kg application of undiluted liquid PEG-20 tallow amine (purity 95%) on the clipped skin of the back.[9] The skin was abraded before the application of the test substance in 1 of the male and 2 of the female rabbits. The exposure sites were occluded with gauze bandages, dental dams, and Elastoplast tape for 24 hours after the application. Rabbits were observed 24 hours and then daily for signs of dermal irritation for 14 days after removing the bandage and excess test substance. Animals with intact exposure sites exhibited slight-to-marked erythema, atonia, and coriaceousness, slight-to-moderate edema, desquamation and fissuring, eschar formation, exfoliation, and subcutaneous hemorrhage and hyperthermia. Rabbits with abraded exposure sites exhibited moderate-to-marked erythema, slight-to-marked atonia and desquamation, slight-to-moderate edema, coriaceousness, and fissuring, and subcutaneous hemorrhage and hyperthermia. During the observation period, 60% of the animals died. The findings upon gross necropsy examination of the 6 surviving animals were not considered to be treatment related. The reported LD_{50} was <2.0 mL/kg for males and females combined.

Polyethylene glycol 50 stearamine. A group of 6 New Zealand white rabbits (n = 3/sex) received a single 2 mL/kg application of 75% (wt/vol) PEG-50 stearamine (purity 99%) in distilled water on the clipped skin of the back.[9] The skin was abraded

before the application of the test substance in 1 of the male and 2 of the female rabbits. The exposure sites were occluded with gauze bandages, rubber dams, and Elastoplast tape for 24 hours after the application. Rabbits were observed 30 minutes and then daily for signs of dermal irritation for 14 days after removing the bandage and excess test substance. All animals survived and appeared normal throughout the study period, except for signs of dermal irritation. The signs included slight-to-moderate erythema and desquamation with slight fissuring and edema. The reported LD_{50} was >1.5 g/kg (males and females combined) in this study.

Repeated-Dose Toxicity

Oral

Polyethylene glycol 2 tallow amine. Groups of 25 young SPF Wistar adult male and female rats were fed PEG-2 tallow amine in the diet (ad libitum) at concentrations of 0, 170, 500, or 1,500 ppm (about 15, 50, and 150 mg/kg/d) for 90 days.[4,5,9] An additional group of 10 male and 10 female rats was given a diet containing 4,500 ppm of the test substance. Further, a group of 7 male and 7 female rats were fed the diet containing 4,500 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 to 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 a diet containing 4,500 ppm of the test substance lost hair and were lethargic throughout the study. At necropsy, there was 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 4,500 ppm group. In this group, microscopic examination revealed engorgement of the *villi* and *lamina propria* of the small intestines with swollen foamy sudanophilic macrophages. The latter macrophages were observed occasionally, and to a lesser degree, in Peyer's patches and regional lymph nodes. The 1,500 ppm group exhibited similar effects, although to a lesser degree than observed in the 4,500 ppm group. Body weight gain was decreased in both the 1,500 ppm group and the 4,500 ppm group, which was attributed to the reduced palatability of the diets. No clinical effects were noted at any dietary concentration less than 4,500 ppm, and no definite hematological abnormality, differences in organ weights, or abnormalities of the reproductive organs were found at any dietary concentration tested. The reported no-observed-effect level (NOEL) was 500 ppm (about 50 mg/kg/d) and the lowest-observed-effect level (LOEL) was 1,500 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%, or 0.5% (wt/wt) for 28 days or until necropsy.[4,5,9,13,29] The test substance was added to the diets as 1% solutions in corn oil. All animals were examined at least once every day for overt toxicity or behavioral changes, individual body weights and group food consumption were recorded weekly, and hematology analyses and necropsy were performed on all rats. The adrenal glands, kidneys, lungs, testes, heart, liver, and ovaries were weighed 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 decreased in males and females at 0.5% and in males at 0.015% in the diet. Feed consumption, hematology, and organ weights were not statistically 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. The no-observed-adverse-effect level (NOAEL) was estimated to be 0.015% (approximately 12 mg/kg/d), based on body weight gain.

Groups of 4 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/d for 90 days.[4,5,9] Body weights were recorded at the beginning of the treatment period and weekly thereafter. Hemoglobin concentrations, packed cell volumes, white cell counts, and differential white cell counts were measured before initiating treatment and immediately before sacrificing the animals at the end of the 90-day treatment period. Blood urea nitrogen levels, serum alkaline phosphatase activity, and 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, urinary bladder, adrenal, ovary and uterus or testes and epididymis, and sciatic nerve. The NOEL was reported to be 13 mg/kg/d, and the LOEL was 50 mg/kg/d. No other findings of this study were presented.

Polyethylene glycol 2 C13-C15 alkyl amine. PEG-2 C13-C15 alkyl amine was tested in rats in a 90-day oral repeated-dose toxicity study.[10] The PEG-2 C13-C15 alkyl amine is not

identified as a cosmetic ingredient in the INCI Dictionary. However, like PEG-2 cocamine and related ingredients, PEG-2 C13-C15 alkyl amine ($x + y = 2$) is a likely analog for these ingredients in a read-across assessment.

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

Polyethylene glycol 15 tallow amine. In a 90-day oral toxicity study, PEG-15 tallow amine was administered in the diet ad libitum to 3 groups of 10 male and 10 female Sprague Dawley rats.[10] The concentrations of the test substance in the test diets were approximately 500, 1,500, or 4,500 ppm (equivalent to about 33, 99, and 292 mg/kg/d for males, respectively, and 40, 123, and 357 mg/kg/d for females, respectively). The control group received the basal diet. Exposure to 1,500 or 4,500 ppm PEG-15 tallow amine caused statistically significant and toxicologically significant effects. At 4,500 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. Feed consumption was also decreased through most of the study. At 1,500 and 4,500 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 or 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 (33-40 mg/kg/d) and the LOAEL was 1,500 ppm (99-123 mg/kg/d) in this study.

POE-5/POP-12 tallow amine. POE-5/POP-12 tallow amine was tested in rats in a 28-day oral repeated-dose toxicity study.[10] This substance is not identified as a cosmetic ingredient in the INCI Dictionary. However, POE-5/POP-12 tallow amine is a likely analog for PEGs cocamine and related ingredients in a read-across assessment. Groups of 5 male and 5 female CD rats received 0, 15, 75, or 200 mg/kg/d 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/d and 200 mg/kg/d groups was attributed to the taste of the test material. Noisy respiration in some of the females receiving 200 mg/kg/d 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 and 200 mg/kg/d was not considered toxicologically significant. At 200 mg/kg/d, 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/d. 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/d 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/d (males) and 200 mg/kg/d (females), and the LOAEL was 200 mg/kg/d (males) based on reduced body weight, body weight gain, and feed conversion efficiency.

Dermal. No systemic toxic effects occurred in rats following a 6-week dermal application study using 10% PEG-15 cocamine.[2]

Polyethylene glycol 2 tallow amine. Two groups of 5 young adult New Zealand white rabbits of each sex were exposed dermally to 0.1% or 0.5% PEG-2 tallow amine dispersed in water.[4,5,9,12,29] The test material was applied to the shaved dorsolumbar region of each animal, 2.0 mL/d, 5 d/wk for 28 days (2 or 10 mg/kg/d). 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, as well as no evidence of systemic toxicity from the clinical and pathology examinations.

Polyethylene glycol 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 for 5 d/wk.[5,9] Initially, the rabbits were treated twice with the 10% solution of the test compound applied to abraded skin. This caused severe erythema, edema, and atonia and mild-to-severe desquamation of the exposed skin. Thus, the concentration was reduced to 2% (wt/vol), and abrasion was discontinued for the remaining 18 treatments. The skin conditions of these animals improved by day 13 and remained relatively constant throughout the remainder of the study. Distilled water was applied to the abraded skin of 10 control rabbits (5 of each sex) for all 20 treatments. Body weights were measured weekly, and hematological analyses and complete necropsies were performed at the end of the study. Liver and kidney weights were measured, and histopathology examinations were performed for several organs, including the treated skin. No treatment-related effects were observed in the skin of the control animals. Body weight losses were reported for 6 of the 10 PEG-20 tallow amine–treated rabbits by the end of the first week of the study, after which a steady weight gain was observed. One animal remained below its initial weight by the end of the study. A normal weight gain pattern was observed in the controls. No biologically significant, treatment-related hematological effects were observed in the treated animals. Necropsy confirmed treatment-related adaptive, cutaneous morphological alterations of the exposed skin, and microscopic examination revealed epidermal and keratin layer thickening. Liver, kidney, and body weights of the treated animals were comparable to those of the controls. Decreased kidney weight in treated females, compared to control females, was not considered to be biologically significant.

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

Reproductive and Developmental Effects

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

Polyethylene Glycol 2 Cocamine

In a combined repeated-dose toxicity study and developmental and reproductive toxicity (DART) screening test, groups of 24 Crl:CD(SD) rats (12 males and 12 females) were fed diets containing 0, 30, 100, 300, or 2,000 ppm PEG-2 cocamine for 14 consecutive days prior to mating (males and females) and throughout gestation and day 4 of lactation (females).[10] The dietary concentrations tested in this study corresponded to dose rates of approximately 0, 2, 8, 23, and 134 mg/kg/d for males and 0, 3, 9, 26, and 148 mg/kg/d 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 2,000 ppm group exhibited increased incidences of red material around the nose, reddened nose, and reddened mouth. At 2,000 ppm, mean body weight was decreased (during the first week of treatment), feed consumption was decreased (throughout the study), and males exhibited decreased liver, kidney, thyroid, and heart weights, which were attributed to the decreases in body weight. The females of the 2,000 ppm group displayed a decreased number of implantation sites and live litter size. The offspring of this group had lower postnatal survival on postnatal days (PNDs) 0, 1, and 4 (and over the period of birth to PND 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 (23-16 mg/kg/d) for parental and developmental effects and 2,000 ppm for reproductive effects in this study. The LOAEL was 2,000 ppm for parental and developmental effects.

Polyethylene Glycol 15 Tallow Amine

In a developmental toxicity study, groups of 25 female Charles River Crl:CDBr rats received 0 (corn oil only), 15, 100, or 300 mg/kg/d PEG-15 tallow amine by gavage from days 6 through 15 of gestation.[10] Developmental parameters measured included numbers of viable fetuses, early and late resorptions, total implantations, total *corpora lutea*, and 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/d group died during gestation. Clinical signs found in the 300 mg/kg/d 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/d and 100 mg/kg/d groups exhibited few or no clinical signs. Body weight, body weight gain, and food consumption were reduced in the 300 mg/kg/d group, but not in the 15 mg/kg/d and 100 mg/kg/d groups (except for a transient statistically significant reduction in food consumption in the 100 mg/kg/d 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/d group appeared to be high, but most of the malformations were found in a single fetus. Among the fetuses of the 300 mg/kg/d group, 1 was missing a urinary bladder, 1 exhibited stenosis of the right carotid artery, 2 had *situs inversus*, and 1 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/d and 100 mg/kg/d 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/d and the developmental NOAEL and maternal LOAEL was 300 mg/kg/d 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 1,000 ppm PEG-15 tallow amine, and a similar group of control rats received the basal diet only.[10] The parental animals of the first generation (F_0) were exposed to the test substance for at least 70 days before mating, and exposure continued until these animals were sacrificed; female F_0 rats were sacrificed on 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/d (males) or 0, 7, 22, or 74 mg/kg/d (females) PEG-15 tallow amine until PND 70. The F_1 animals selected for breeding from the high-dose group were fed 1,000 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; body weights, body weight gains, food consumption, and absolute and relative organ weights were measured. Blood samples were collected from 1 F_1 male and 1 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 1,000 ppm (65-66 mg/kg/d), and the NOAEL for developmental and reproductive effects was 300 ppm (15-17 mg/kg/d) in this study.

Genotoxicity

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

PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test. At concentrations up to 150 g/L, PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay.[2]

Table 11 summarizes 10 genotoxicity studies of several PEGs cocamine ingredients and 1 ingredient analog (ie, PEG-8 stearamine), including 7 in vitro tests (PEG-2 tallow amine, PEG-8 stearamine, PEG-15 tallow amine, and PEG-20 tallow amine) and 3 in vivo tests (PEG-2 tallow amine, PEG-15 tallow amine, and PEG-20 tallow amine). The results were generally negative, except that 1 of the 4 in vitro tests of PEG-20 tallow amine produced a concentration-dependent (0.05-0.3 µl/mL) increase in the numbers of chromosomal aberrations in Chinese hamster ovary cells with metabolic activation.[9]

In addition, an acute dosage of PEG-2 tallow amine (10,860 mg/kg by gavage) in a mouse micronucleus test yielded a statistically significant increase in the number of micronucleated polychromatic erythrocytes 24 hours (but not 48 or 72 hours) after exposure, as well as overt signs of toxicity.[9] The increase

Table 11. Genotoxicity Studies.

Test substance	Concentration/dose (vehicle)	Method	Results	Reference
In vitro				
PEG-2 tallow amine	Up to 0.08 μL/plate with and without metabolic activation (ethanol)	Ames test on Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538; positive controls: 2-nitrofluorene, 1,2-propane sultone, and 9aminoacridine	Not mutagenic	4,5,9
PEG-8 stearamine	0.0008-0.08 μL/plate with and without metabolic activation (water)	Ames test on Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538; positive controls: 2-nitrofluorene, 1,2-propane sultone, and 9aminoacridine	Not mutagenic	9,11,29
PEG-15 tallow amine	Up to 300 μg/plate without metabolic activation; up to 1000 μg/plate with metabolic activation (not specified)	Ames test on Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538; Positive controls not specified	Not mutagenic	10
PEG-20 tallow amine	Up to 0.08 μL/plate with and without metabolic activation (water)	Ames test on Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538; Positive controls: 2-nitrofluorene, 1,2-propane sultone, and 9aminoacridine	Not mutagenic	4,5,9
PEG-20 tallow amine (purity 99.5%)	0.33, 1.0, 3.3, 10, 33, and 100 μg/plate with and without metabolic activation (ethanol)	Mouse lymphoma mutation assay on $TK^{+/-}$ L5178Y cells; positive controls not specified	Not mutagenic	4,5,9
PEG-20 tallow amine	Up to 0.03 μL/mL without metabolic activation and up to 0.3 μL/mL with metabolic activation	Cell chromosome aberrations test on Chinese hamster ovary cells; positive controls: triethylenemelamine and cyclophosphamide	Numbers of aberrations appeared to be elevated without metabolic activation, but no concentration–response relationship detected Concentration-dependent increase in numbers of chromosome aberrations with metabolic activation	4,5,9
PEG-20 tallow amine	0.008×10^{-4} to 0.23×10^{-4} μL/mL (ethanol)	Unscheduled DNA synthesis (UDS) test on freshly prepared primary rat hepatocytes; positive control: 7,12-dimethylbenz[a]anthracene dissolved in dimethyl sulfoxide	Not mutagenic	4,5,9
In vivo				
PEG-2 tallow amine	10 860 mg/kg by gavage (distilled water)	Mouse micronucleus (MN) assay (performed in accordance with OECD methods and guidelines) on groups of 30 mice (15 of each sex/group) given a single dose of PEG-2 tallow amine; 2 additional groups of 30 mice (15 of each sex/group) served as controls; positive control: one of the control groups received mitomycin C by intraperitoneal (ip) injection	Statistically significant increase in number of micronucleated polychromatic erythrocytes 24 hours, but not 48 or 72 hours, after exposure to PEG-2 tallow amine, not considered treatment related because well within the ranges of historical controls; Ratio of polychromatic to normochromatic erythrocytes statistically significantly reduced 24, 48, and 72 hours after exposure, suggesting treatment-related toxicity to bone marrow cells Clinical signs 72 hours after exposure: slight pallor of the extremities, diarrhea, slight to moderate piloerection, lethargy, decreased respiratory rate and ptosis, walking on toes, and greasy fur; one male animal died about 30 hours after treatment	4,5,9
PEG-15 tallow amine	100 mg/kg (not specified)	Mammalian MN assay (species tested not specified)	Not mutagenic	10
PEG-20 tallow amine	39, 130, or 390 mg/kg/d by gavage for 5 consecutive days (distilled water)	Cytogenicity study on groups of 10 Sprague Dawley rats (5 of each sex/group) given PEG-20 tallow amine by gavage for 5 consecutive days; 2 additional groups of 10 rats (5 of each sex/group) served as controls; positive control: one control group received methylmethane sulfonate by gavage	Not mutagenic All animals exposed to 390 mg/kg/d and 2 females exposed to the lower dose rates developed diarrhea; some treated animals exhibited red-brownish exudates around the eyes and mouth, but this was not considered to be treatment related	4,5,9

Abbreviation: OECD, Organisation for Economic Co-operation and Development; PEG, polyethylene glycol.

in micronucleated cells at 24 hours was not considered to be treatment related because the increase was well within the range of historical controls. However, the ratio of polychromatic to normochromatic erythrocytes was statistically significantly reduced 24, 48, and 72 hours after exposure to the test substance, suggesting treatment-related toxicity to bone marrow cells at the dose tested.

Carcinogenicity

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

Irritation and Sensitization

PEG-2 cocamine was classified as a moderate cutaneous irritant, and PEG-15 cocamine was considered a mild irritant. PEGs were nonirritating to the skin of rabbits and guinea pigs, and PEG-75 was not a sensitizer, PEG-2 cocamine was considered an ocular irritant, and PEG-15 cocamine caused corneal irritation. In clinical studies, PEG-8 was a mild sensitizer and irritant. Contact dermatitis and systemic toxicity in burn patients were attributed to a PEG-based topical ointment. Bar soaps containing 13% coconut oil, when tested using Draize procedures, produced minimal skin reactions.[2]

Nonhuman

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

Polyethylene glycol 2 tallow amine. Five young adult New Zealand white rabbits of each sex were treated with 0.1% or 0.5% PEG-2 tallow amine dispersed in water.[4,5,9,12] The test substance was applied to the shaved dorsolumbar region of each animal, 2.0 mL/d, 5 d/wk 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 were 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. Of the 10 rabbits in the 0.1% group, 5 exhibited slight edema 2 days after the initiation of treatment, and 2 of these 5 animals developed moderate erythema within 5 days of treatment. Slight edema, desquamation, and wrinkled skin were observed in most animals of the 0.1% group. A few rabbits in the control group exhibited minor histological anomalies in the skin at the application site.

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

In contrast, PEG-2 tallow amine appeared to be sensitizing to mice in a local lymph node assay (LLNA).[31] In this test, 0.1%, 0.3%, or 1.0% PEG-2 tallow amine, or 0.25% dinitrochlorobenzene (DNCB), 50% (vol/vol) hexyl cinnamal (HCA), or 25% sodium lauryl sulfate (SLS) was applied topically once daily to the dorsum of the ear for 3 consecutive days (wt/vol,

except where indicated; solvent not specified). The PEG-2 tallow amine exposure was associated with a substantial increase in ear thickness and a dose-dependent increase in lymph node cell proliferation (maximum stimulation index [SI] = 125.9; EC3 <0.1%). In comparison, the known sensitizers DNCB and HCA yielded SIs of 104.6 and 30.1, respectively. Treatment with the higher doses of PEG-2 tallow amine (ie, 0.3% and 1.0%) or either of the positive control substances was associated with substantially increased B cell to T cell (B:T) ratios and percentages of $Ia^+/CD69^+$ cells. Treatment with SLS produced substantial ear swelling and an SI of 3.2, but no increase in cellular markers. The summary states that, although PEG-2 tallow amine was very irritating, the magnitude of the cellular responses indicates that dermal application of this substance may be sensitizing.

Human

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

In the other test, a leave-on hair styling formulation containing 1.0% PEG-15 cocamine was not sensitizing in 212 participants.[32] During the induction phase of the study, the formulation was applied neat to the skin of normal participants, and the application site was covered with a semiocclusive 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.

Polyethylene glycol 5 soyamine. A hair dye formulation containing 3.4% PEG-5 soyamine caused transient mild-to-moderate signs of irritation in an open application patch test.[34,35] A single 0.5 mL of the undiluted formulation was applied to the inner forearm of each of 12 healthy participants (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/persulfate 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 participants) and a phototoxicity study (22 participants) were submitted to CIR in 2011.[4,36,37] In these studies, no photoallergic or other phototoxic effects were found in the skin after exposure to an adult sunscreen formulation containing 2.9% PEG-15 cocamine (no details of these studies were provided).

Application of the Framework to Evaluate PEGs Cocamine Ingredients

The framework for identifying and evaluating analogs applied in this safety assessment is described and explained in several publications,[3,7,36,38] including one paper that illustrates the application of the framework for assessing the safety of the PEGs cocamine ingredients that are specifically derivatives of coconut oil.[7] The read-across analysis evaluated by the Panel covers the entire group of PEGs cocamine and related ingredients, including the derivatives of soy and rapeseed oil and tallow and the other fatty acids from which the ingredients of this group are manufactured.

Analog Selection

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

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

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

Four PEGs cocamine were selected as the structures of interest (SOIs) to cover the range of PEG side chain lengths for identifying analogs. The alkyl amine chain length and degree of unsaturation were considered when evaluating the suitability of the analogs identified for each of these 4 PEGs cocamine. The 4 PEGs cocamine selected as SOIs are:

- PEG-2 cocamine (analog group 1)
- PEG-4 cocamine (analog group 2)
- PEG-10 cocamine (analog group 3)
- PEG-15 cocamine (analog group 4)

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

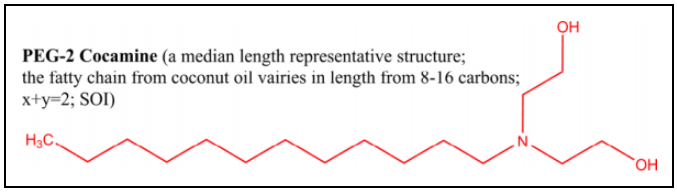


Figure 4. Polyethylene glycol (PEG)-2 cocamine (C12).

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

Polyethylene glycol 2 cocamine (analog group 1). The structure of one major component of PEG-2 cocamine is presented in Figure 4.

The structures of the 3 analogs identified initially for PEG-2 cocamine are illustrated in Figure 5.

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

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

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

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

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

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

Polyethylene glycol 4 cocamine (analog group 2). The structure of one major component of PEG-4 cocamine is presented in Figure 6.

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

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

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

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

- The presence of *N*-hydroxyethyl groups of the analog, rather than the diethoxylate groups in PEG-4 cocamine, may yield divergent metabolic fate and toxicity pathways for these substances.
- The alkyl chain length distributions of the analog and PEG-4 cocamine overlap, and the difference in the distributions is not expected to cause significant differences in the toxicity profiles of these substances.
- The tallow moieties of the analog have greater degrees of unsaturation, and consequently greater susceptibility to epoxidation and hydroperoxidation, than the coconut oil moieties of PEG-4 cocamine. Thus, this analog is conservative for PEG-4 cocamine.

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

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

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

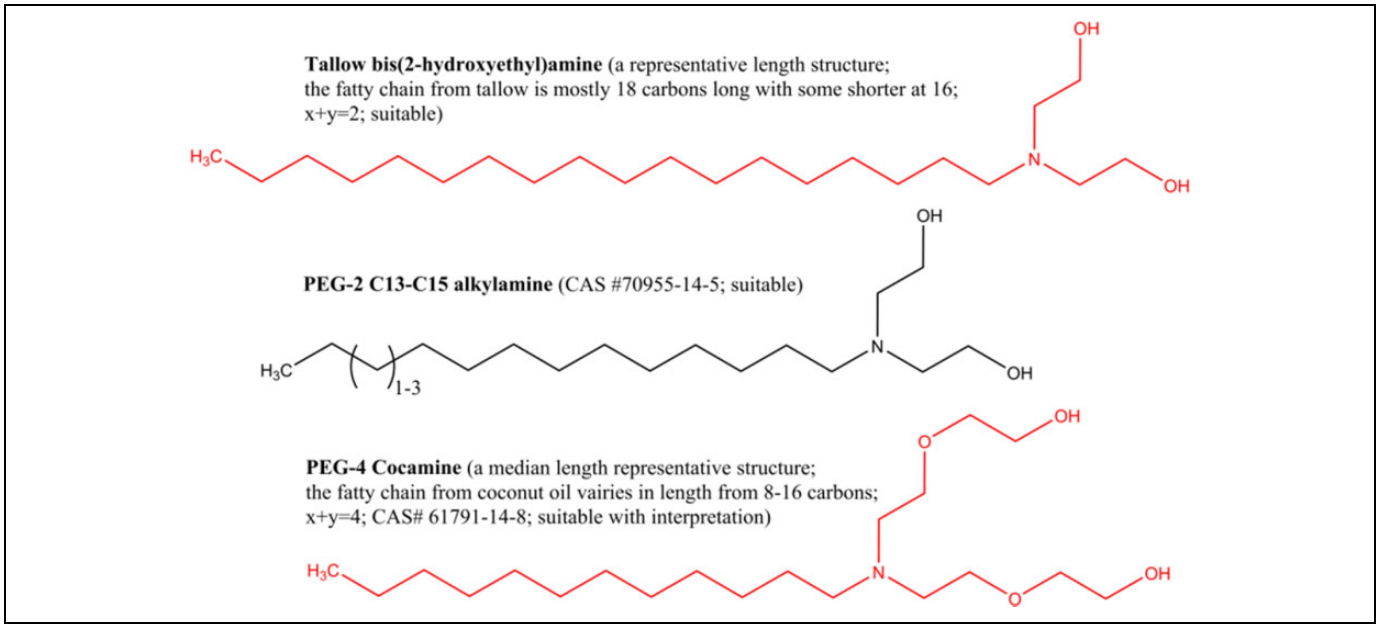


Figure 5. Analogs identified for polyethylene glycol (PEG)-2 cocamine.

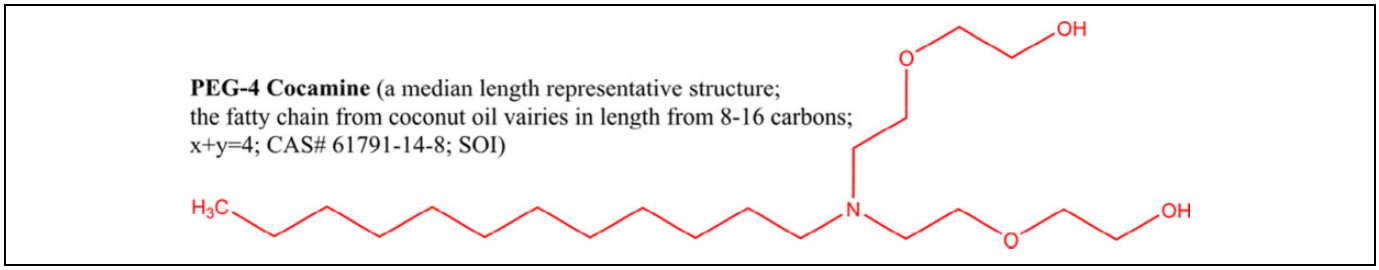


Figure 6. Polyethylene glycol (PEG)-4 cocamine (C12).

- 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.

Polyethylene glycol 10 cocamine (analog group 3). The structure of one major component of PEG-10 cocamine is presented in Figure 8.

The structures of the 4 analogs identified initially for PEG-10 cocamine are illustrated in Figure 9.

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

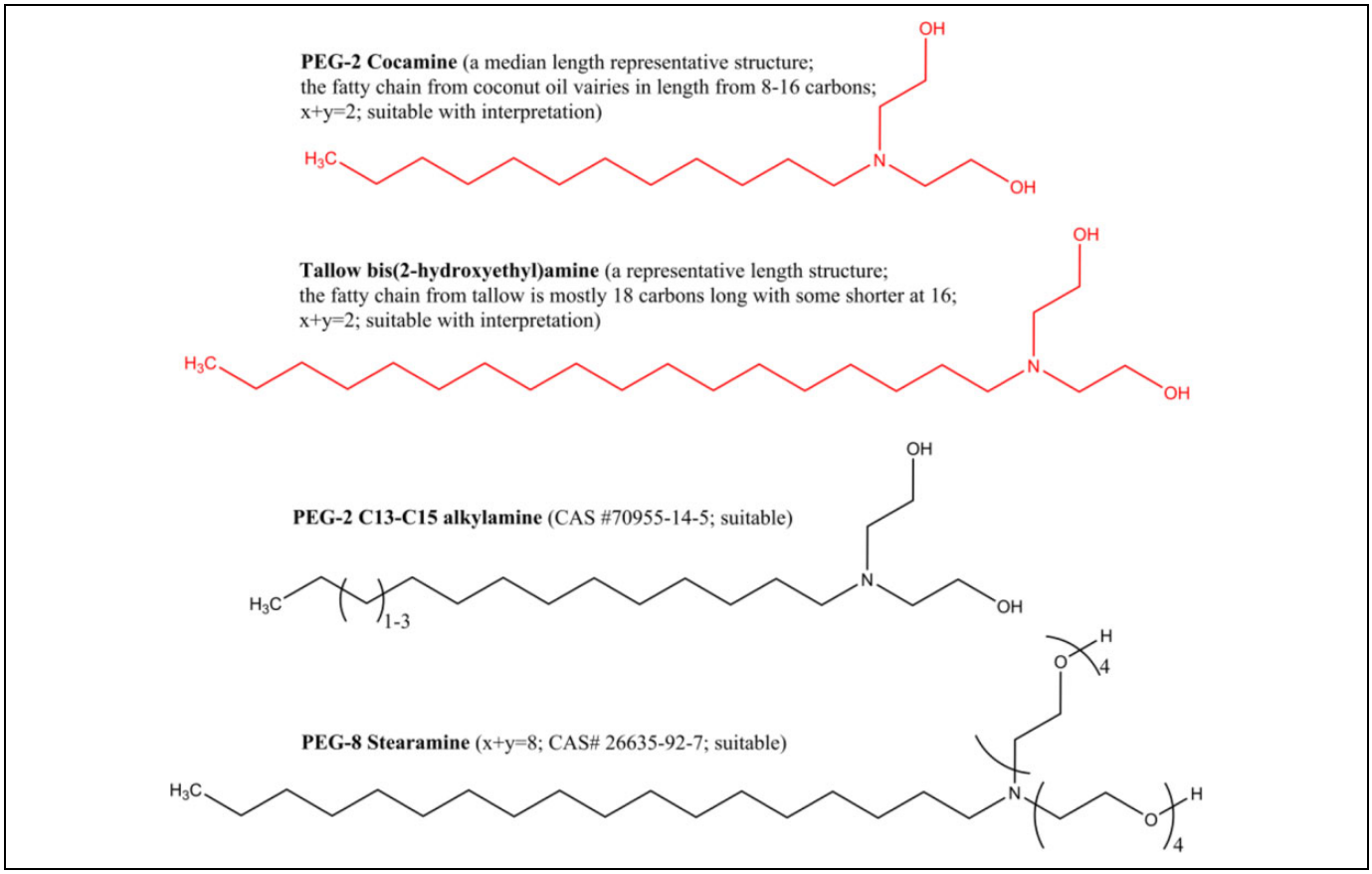


Figure 7. Analogs identified for polyethylene glycol (PEG)-4 cocamine.

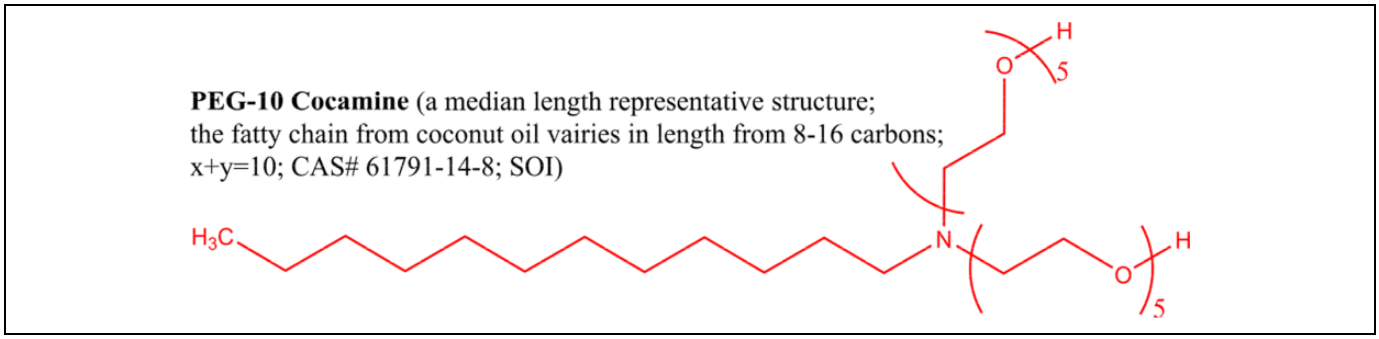


Figure 8. Polyethylene glycol (PEG)-10 cocamine (C12).

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:

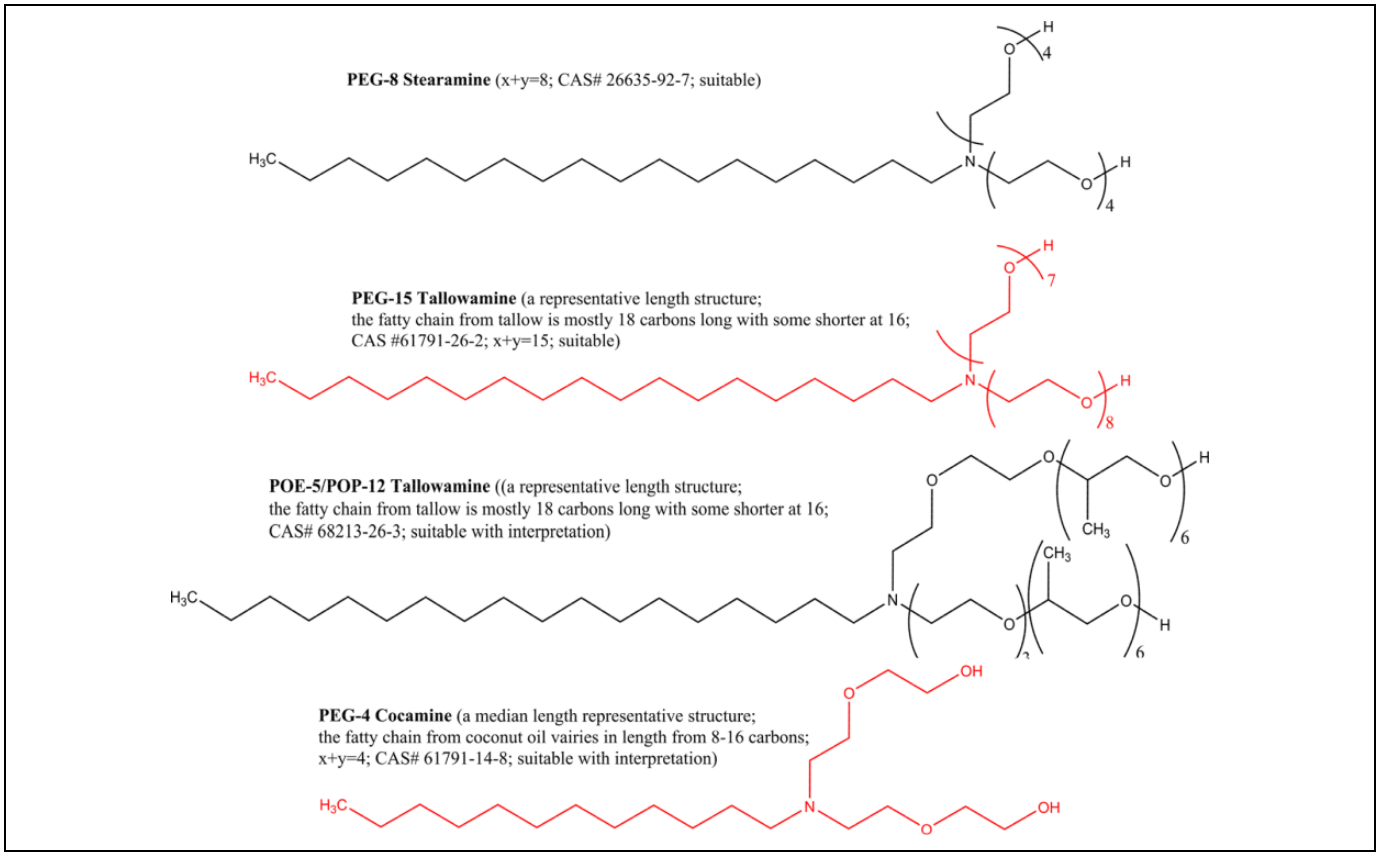


Figure 9. Analogs identified for polyethylene glycol (PEG)-10 cocamine.

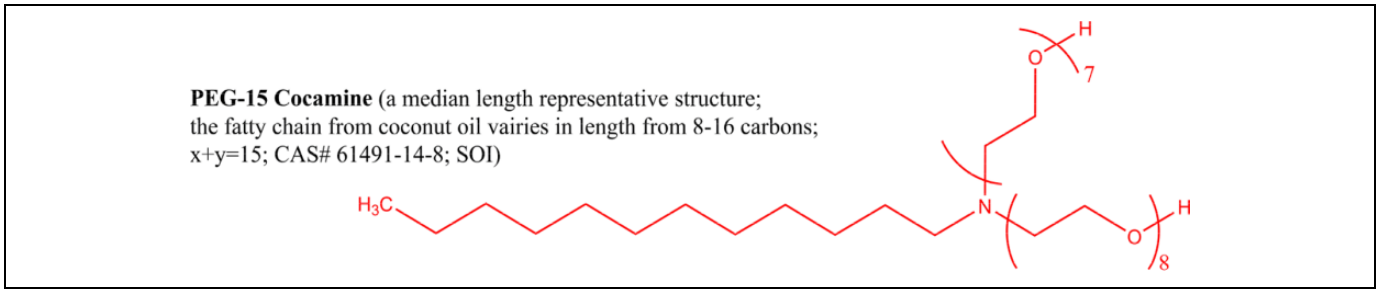


Figure 10. Polyethylene glycol (PEG)-15 cocamine (C12).

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

Polyethylene glycol 15 cocamine (analog group 4). The structure of one major component of PEG-15 cocamine is presented in Figure 10.

The structures of the 5 analogs identified initially for PEG-15 cocamine are illustrated in Figure 11.

Polyethylene glycol 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 degrees 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.

Polyethylene glycol 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.

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

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

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

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

Chemical Structure

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

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

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

DEREK for Windows Rapid Prototype Alert Notation

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

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

The Panel has evaluated the available data on triethylene glycol and other PEGs with average $x + y > 2$, including the reports of renal toxicity when PEGs have been used on severely damaged skin, as in burn patients.[18] The Panel determined that the PEGs are not metabolized to ethylene glycol, at least under normal homeostasis, and oral and dermal toxicity studies of the PEGs yielded no evidence of the type of nephrotoxicity produced by ethylene glycol and diethylene glycol. The 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

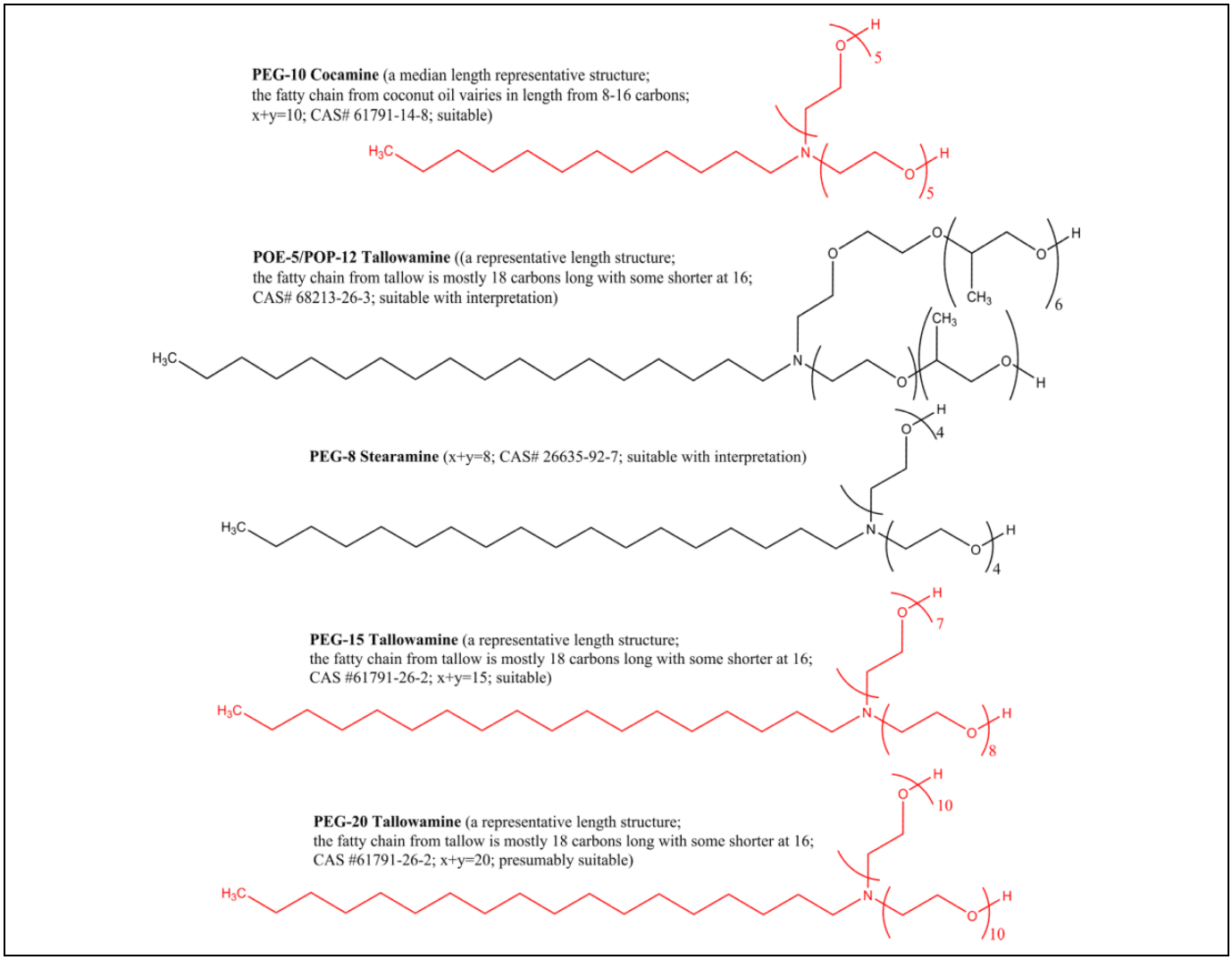


Figure 11. Analogs identified for polyethylene glycol (PEG)-15 cocamine.

rinse-off products and that there is a large margin of safety for leave-on products containing PEGs, after reviewing PEG-4 dermal penetration data for normal skin and skin in which the stratum corneum was removed.

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

Physicochemical Properties

There are substantial differences in physicochemical properties across the PEGs cocamine SOIs and their corresponding analogs. These differences would undoubtedly affect bioavailability in a manner dependent on the route of exposure. The longer alkyl chain lengths derived from the fatty acids of tallow or hydrogenated tallow and longer polyethoxy chains are generally expected to reduce bioavailability, compared to the shorter alkyl chain lengths derived from the fatty acids of coconut oil and shorter polyethoxy chains. However, longer polyethoxy chain lengths will be associated with greater polarity, which may offset the effect of the greater molecular weight of the tallow-derived analogs to some extent.

Chemical Reactivity

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

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

However, the ether linkage is isosteric with a $–CH_2–$linkage. Isosteric substituents have similar molecular shapes and

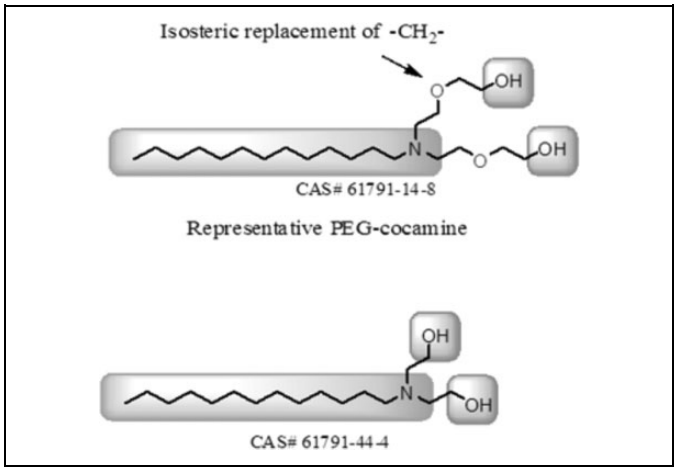


Figure 12. Isostericity of ether and methylene linkages.

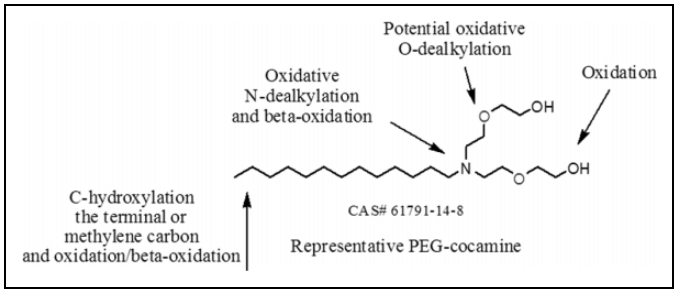


Figure 13. Theoretical metabolic transformations of polyethylene glycols (PEGs) cocamine ingredients.

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.

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

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

The metabolism of the polyethoxylate groups in PEGs cocamine is anticipated to be similar to the metabolism of PEGs. The PEGs are excreted mainly unchanged in the urine and feces after oral or intravenous exposure.[37,39] The extent of metabolism depends on molecular weight; there is little or no metabolism of PEGs with molecular weights >5,000 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).

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 $x + y \geq 8$). Ethylene glycol has not been shown to be formed as a metabolite of the PEGs.

An additional consideration, as noted above, is that the unsaturated fatty acids of tallow (not hydrogenated tallow) in the structure of some of the ingredients and analogs may be metabolized to form epoxide metabolites. The PEGs cocamine and related structures that have no unsaturated fatty acid amine moieties do not have this potential.

None of the final metabolites of PEG-4 cocamine were predicted to be of toxicological concern using computational tools. The PEG-4 cocamine was chosen in 2 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.

Polyethylene glycol 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.

In Figure 16, the oxidation of ethoxyl ethanol may yield the corresponding carboxylic acid-bearing metabolite (3) through an aldehyde intermediate (2). The enzymes that catalyze the metabolism of primary alcohols to aldehydes, and then to carboxylic acid, have broad substrate specificity. Subsequently, metabolite (3) could be glucuronidated to yield metabolite (4).

The oxidative *N*-dealkylation of (1) may yield metabolites (5), (6), (8), and (9). Oxidative *N*-dealkylation (also known as deamination) involves hydrogen abstraction and oxygen addition (hydroxylation) at a carbon atom α to the nitrogen atom. The further metabolic oxidation of aldehydes (6) and (8) results in carboxylic acids (7) and (10).

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.

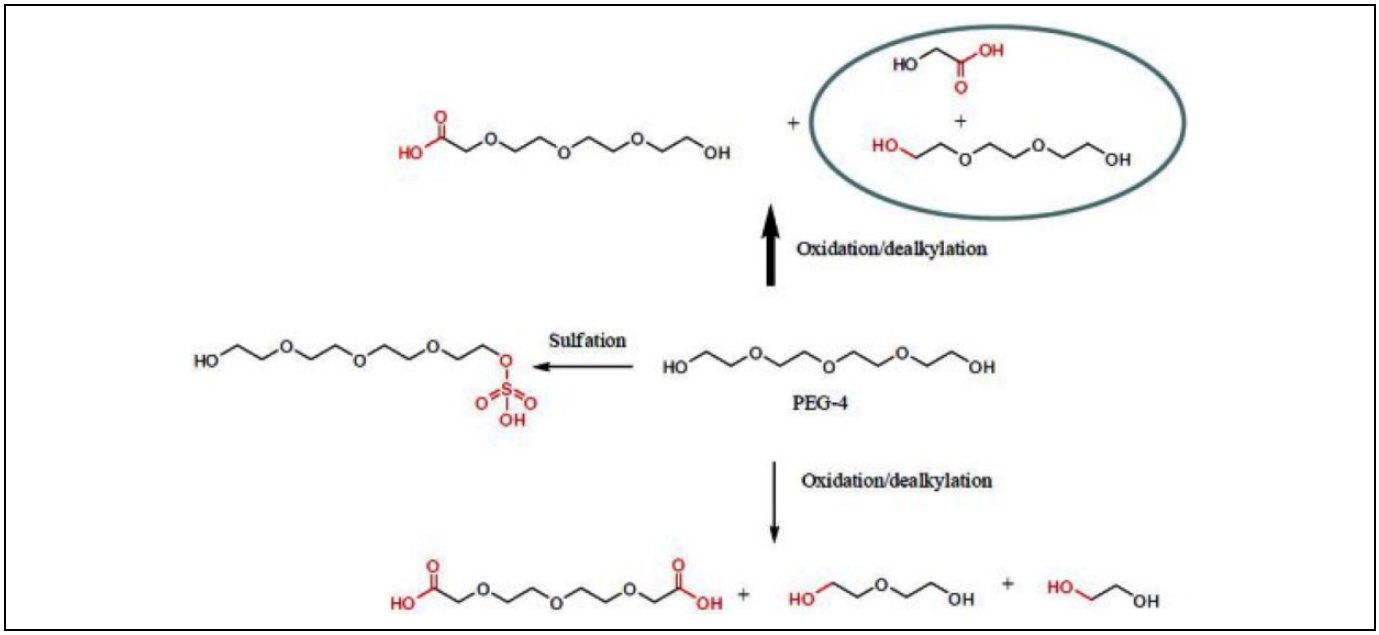


Figure 14. Metabolism of polyethylene glycols (PEGs).

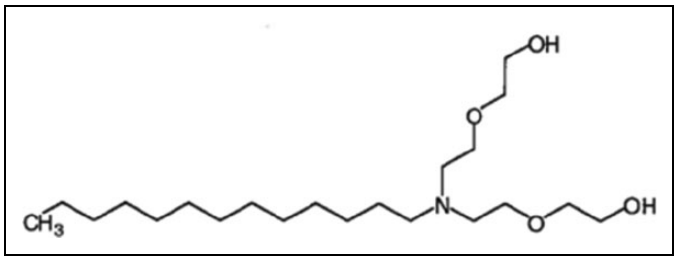


Figure 15. Polyethylene glycol (PEG)-4 cocamine structure evaluated in the first case study.

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.lhasalimited.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 and the potential dermal interactions are presented in Figure 18.

- The authors noted that PEG-4 cocamine has a molecular weight of 277 and an estimated log *P* of 1.961, suggesting 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

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

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 monoamine oxidase A are expressed only at a low level
- Cytochromes P-450 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, *N*-acetyl transferase, and catechol-*o*-methyl transferase

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

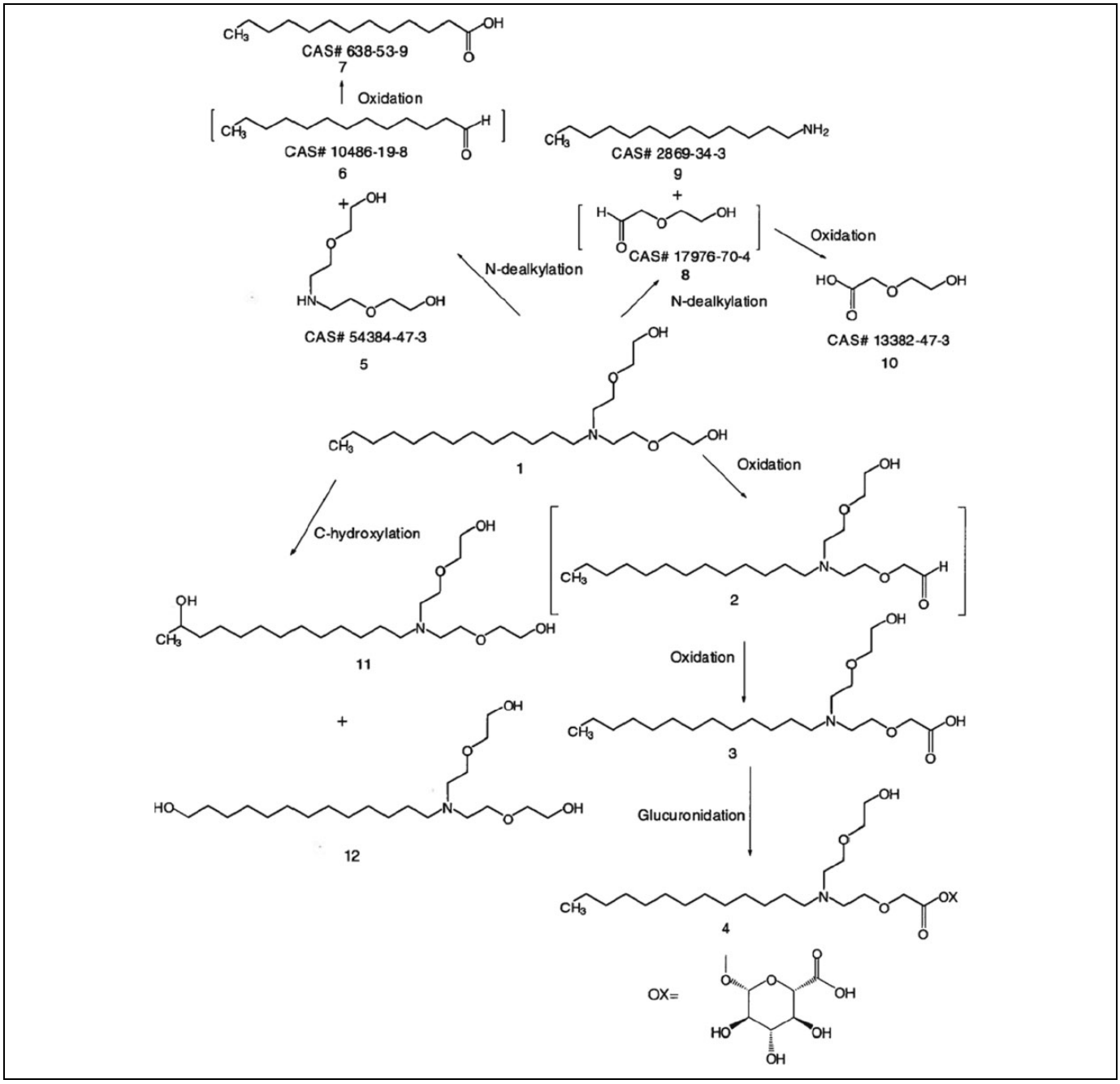


Figure 16. Predicted major metabolites of a polyethylene glycol (PEG)-4 cocamine in the first case study.

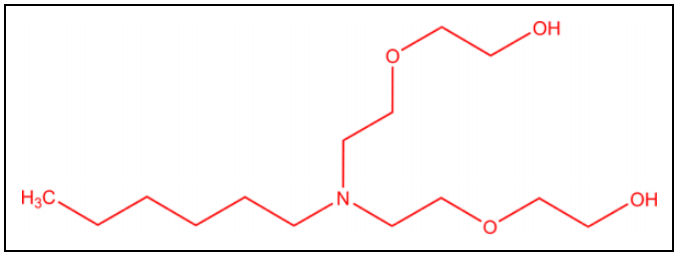


Figure 17. Polyethylene glycol (PEG)-4 cocamine structure evaluated in the second case study.

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. CYP1 and 3 families of biotransformation

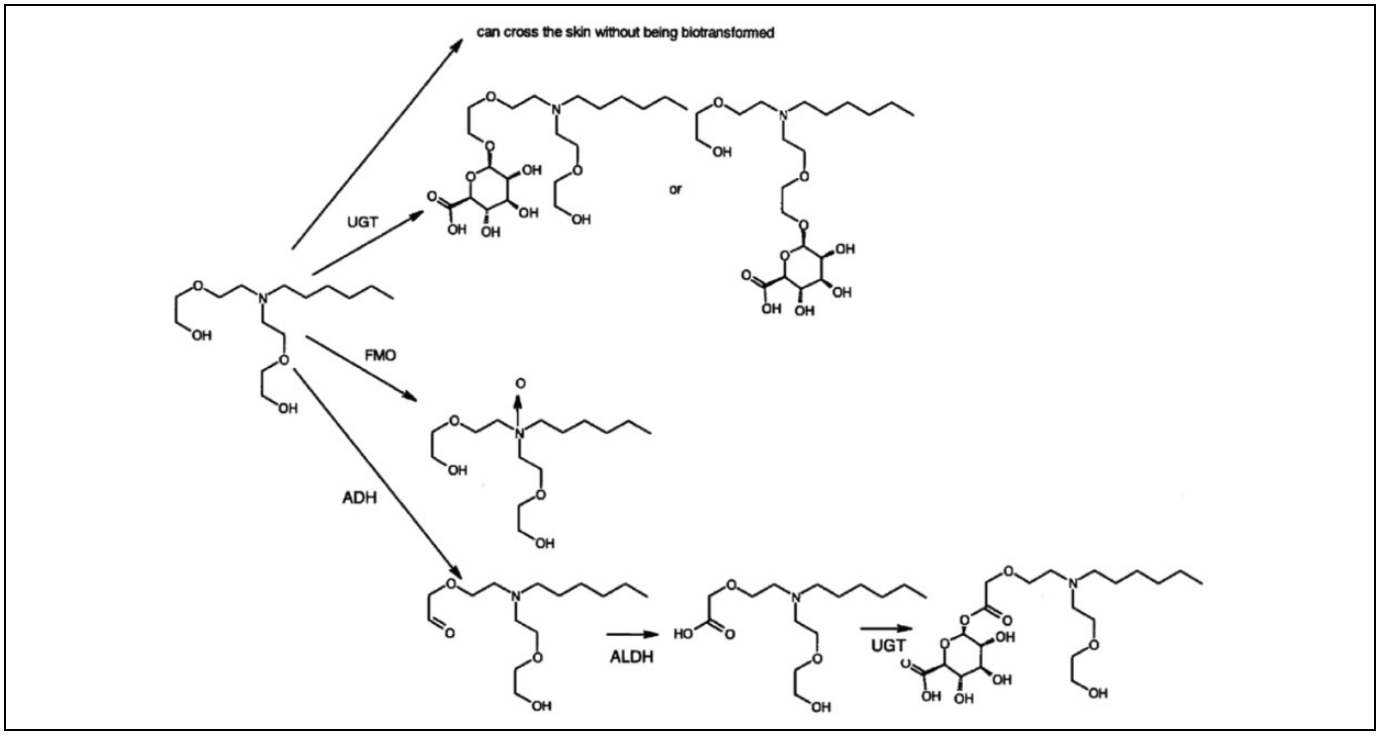


Figure 18. Plausible metabolism of a polyethylene glycol (PEG)-4 cocamine in the skin, from the second case study.

enzymes are expressed at low levels in the skin, but are highly expressed and functional in the liver.

On the other hand, an increase in 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 3 levels on or in the skin (Figure 19):[4]

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

Analog Toxicity Data Review

Tables 12 to 15 summarize the toxicological data available for the analogs identified for each of the 4 PEGs cocamine selected as SOIs. The data provided in these tables (and described in greater detail in the appropriate sections of this report) address repeated-dose toxicity, genotoxicity, and DART as toxicological end points. Note that a rat DART screening test was identified for PEG-2 cocamine (Tables 12 and 13).

Oral repeated-dose toxicity. Oral repeated-dose toxicity studies, including 28- and 90-day studies, have been conducted in rats and dogs with tallow-derived analogs that cover $x + y = 2$ (ie, 3 studies for PEG-2 tallow amine; Tables 12 and 13) and $x + y =$ 15 to 17 (ie, 2 studies, each for PEG-15 tallow amine and POE-5/POP-12 tallow amine; Tables 14 and 15). In addition, a 90-day rat study and 90-day dog study of the analog PEG-2 C13-C15 alkyl amine ($x + y = 2$) were performed (Tables 12 and 13). These studies showed local effects on the gastrointestinal tract, but little or no evidence of other treatment-related effects. No evidence of nephrotoxicity was observed in any of these studies. The studies are reasonably consistent in their reported NOAELs or NOELs, given the variety of dose ranges tested in these studies.

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

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

In several of the oral studies, histiocytosis (the presence of foamy macrophages) was noted in the small intestines and mesenteric lymph nodes of the test animals. The prevailing scientific opinion is that, without additional

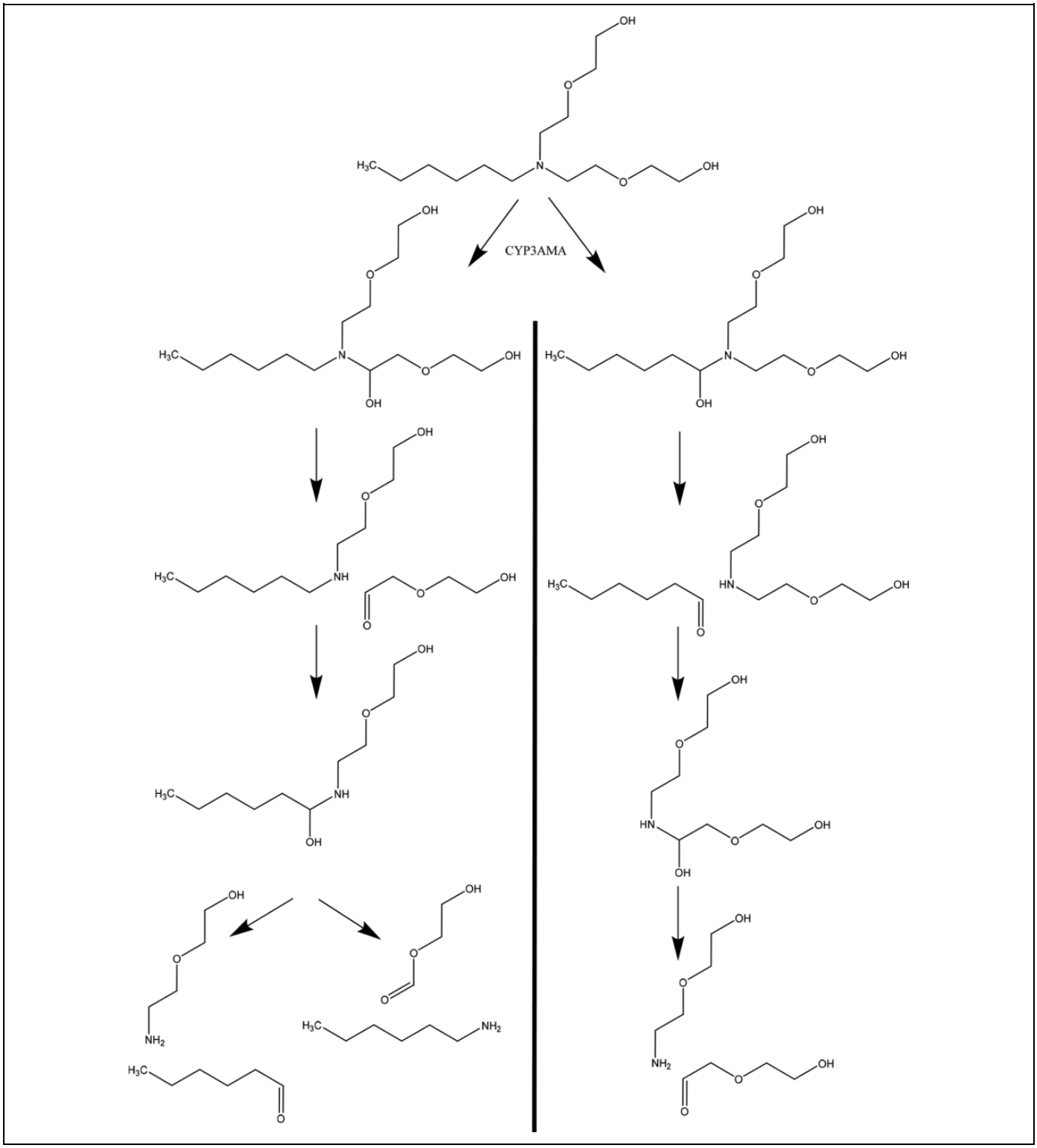


Figure 19. Possible *N*- or *O*-dealkylations in the skin (major in the liver).

evidence of concurrent toxicity, the presence of foamy macrophages in organs such as the intestine should not be considered an adverse effect.[40-43] These lesions are attributable to the clearance of oils with high molecular weight and are not associated with long-term effects.[41-43] Furthermore, as the authors suggested, histiocytosis in the small intestines and mesenteric lymph nodes observed in a repeated-dose oral toxicity study does not represent well the intended route of human exposure (dermal) for use of the PEGs cocamine ingredients in cosmetic products.[5]

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

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-dose toxicity	Developmental and reproductive toxicity (DART)	Reference
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/d (males) or 3, 9, 26, 148 mg/kg/d (females) via diet for 69-72 days. Developmental NOAEL = 23 mg/kg/d. Decreased postnatal survival, live litter size, # of pups born, and implantation sites. Reproductive NOAEL = 134 mg/kg/d (highest dose tested). Parental NOAEL = 23 mg/kg/d	10
Analogs							
PEG-2 tallow amine	61791-44-4	14-18	2	Ames test: (−) In vivo mouse micronucleus test: (−)	*Rat 90-day oral study*. 15, 50, or 150 mg/kg/d via diet; NOEL = 50 mg/kg/d. Palatability of diet decreased at high dose. Gross macroscopic observations: yellow coloration and thickening of mucosa in small intestine and regional mesenteric lymph nodes at high dose; histiocytosis in small intestine and mesenteric lymph nodes at mid and high dose *Rat 90-day oral study*. 0.8, 12, or 400 mg/kg/d via diet; NOEL = 12 mg/kg/d (based on body weight gain) or 40 mg/kg/d (based on histiocytosis). Food consumption in all treated groups similar to control. Small decrease in body weight gain in mid-dose males and high-dose males and females; histiocytosis in small intestine and mesenteric lymph nodes at high dose *Dog 90-day oral study*. 13, 40, or 120 mg/kg/d via diet; NOEL = 13 mg/kg/d. Palatability issues at mid and high dose. GI clinical signs at mid and high dose (vomiting); histiocytosis in small intestine and regional lymph nodes at mid and high dose *Rabbit 28-day percutaneous study*. 0.1% or 0.5% aqueous dispersion (2 or 10 mg/kg/d), 5 d/wk for 4 weeks. Slight to moderate skin irritation at both concentrations; no evidence of systemic toxicity	No data	9,12,13
PEG-2 C13-C15 alkyl amine	70955-14-5	13-15	2	No data	*Rat 90-day oral study*. 15, 30, or 150 mg/kg/d via gavage; NOAEL = 15 mg/kg/d. Macro and microscopic changes in nonglandular stomach *Dog 90-day oral study*. 15, 30, or 100 mg/kg/d via capsule; NOAEL = 30 mg/kg/d. GI clinical signs: increased alanine aminotransferase (ALT) females only; increased pigment accumulation in Kupffer cells and bile canaliculi females only		10
PEG-4 cocamine	61791-14-8	8-16	4	No data	No data	No data	-

Abbreviations: GI, gastrointestinal; NOEL, no-observed-effect level; PEG, polyethylene glycol.

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

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-dose toxicity	Developmental and reproductive toxicity (DART)	Reference
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/d (male) or 3, 9, 26, 148 mg/kg/d (female) via diet for 69-72 days via diet; developmental NOAEL 23 mg/kg/d; decreased postnatal survival, live litter size, # of pups born, implantation sites; reproductive NOAEL 134 mg/kg/d (highest dose tested); parental NOAEL 23 mg/kg/d	10
PEG-2 tallow amine	61791-44-4	16-18	2	Ames test: (−) In vivo mouse micronucleus test: (−)	*Rat 90-day oral study*. 15, 50, or 150 mg/kg/d via diet; NOEL = 50 mg/kg/d. Palatability of diet decreased at high dose. Gross macroscopic observations: yellow coloration and thickening of mucosa in small intestine and regional mesenteric lymph nodes at high dose; histiocytosis in small intestine and mesenteric lymph nodes at mid and high dose *Rat 90-day oral study*. 0.8, 12, or 400 mg/kg/d via diet; NOEL = 12 mg/kg/d (based on body weight gain); 40 mg/kg/d (based on histiocytosis). Food consumption in all treated groups similar to control. Small decrease in body weight gain in mid-dose males and high-dose males and females; histiocytosis in small intestine and mesenteric lymph nodes at high dose *Dog 90-day oral study*. 13, 40, or 120 mg/kg/d via diet; NOEL = 13 mg/kg/d. Palatability issues at mid and high dose. GI clinical signs at mid and high dose (vomiting); histiocytosis in small intestine and regional lymph nodes at mid and high dose *Rabbit 28-day percutaneous study*. 0.1% or 0.5% aqueous dispersion (2 or 10 mg/kg/d), 5 d/wk. Slight (to moderate) skin irritation at both concentrations. No evidence of systemic toxicity	No data	9,12,13
PEG-2 C13-C15 alkyl amine	70955-14-5	13-15	2	No data	*Rat 90-day oral study*. 15, 30, or 150 mg/kg/d via gavage; NOAEL = 15 mg/kg/d. Macro and microscopic changes in nonglandular stomach *Dog 90-day oral study*. 15, 30, or 100 mg/kg/d via capsule; NOAEL = 30 mg/kg/d. GI clinical signs: Increased ALT in females only; Increased pigment accumulation in Kupffer cells and bile canaliculi in females only	No data	10
PEG-8 stearamine	26635-92-7	16-18	8	Ames test: (−)	No data	No data	9,11

Abbreviations: ALT, aminotransferase; GI, gastrointestinal; NOEL, no-observed-effect level; PEG, polyethylene glycol.

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

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

Abbreviations: GI, gastrointestinal; NOEL, no-observed-effect level; PEG, polyethylene glycol.

Dermal repeated-dose toxicity. Dermal 28-day repeated-dose toxicity studies have been conducted in rabbits with tallow PEG-2 tallow amine ($x + y = 2$; 1 study; Tables 12 and 13) and PEG-20 tallow amine ($x + y = 20$, 2 studies; Table 15). Local skin irritant effects were noted in these studies, but there was no evidence of systemic toxicity.

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

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

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

Polyethylene glycol 20 tallow amine was negative in an Ames test, an in vitro mouse lymphoma assay, and an in vitro unscheduled DNA synthesis assay (Table 15). An in vitro chromosomal 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 chromosomal aberration assay in mice (Table 15). The authors also noted that PEG-2 tallow amine ($x + y = 2$) was negative in an in vivo mouse micronucleus assay (Tables 12 and 13).[5]

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

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

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

Reproductive and developmental toxicity. Reproductive and developmental toxicity data are available for:

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

No evidence of a teratogenic effect was observed in any of the studies. Reproductive toxicity studies of the analogs showed effects on reproductive performance at doses that were

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

Chemical	CAS No.	R	x + y	Genotoxicity	Repeated-dose toxicity	Developmental and reproductive toxicity (DART)	Reference
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/d via gavage. NOAEL = 75 mg/kg/d. Decreased body weight gain and food consumption	No data	[10]
PEG-8 stearamine	26635-92-7	16-18	8	Ames test: (−)	No data	No data	[9,11]
PEG-15 tallow amine	61791-26-2	16-18	15	Ames test: (−) In vivo mouse micronucleus test: (−)	*Rat 90-day oral study*. 33, 99, and 292 mg/kg/d via diet. NOEL = 33 mg/kg/d. GI irritation, histiocytosis in small intestine and mesenteric lymph nodes at mid and high dose	*Rat developmental toxicity study*: 15, 100, or 300 mg/kg/d via gavage on gestation days 6-15. NOAEL 300 = mg/kg/d *Rat 2-generation DART study*. NOAEL = 15 mg/kg/d; NOAEL = 15 mg/kg/d; LOAEL = 53 mg/kg/d. Litter loss, decreased litter size, and postnatal survival	[10]
PEG-20 tallow amine	61791-26-2	16-18	20	Ames test: (−) In vitro mouse lymphoma test: (−) In vitro UDS test: (−) In vitro chromosome aberration test: (−) without S-9; (+) with S-9 In vivo mouse chromosome aberration test: (−)	*Rabbit 28-day percutaneous study*: 10% aqueous dispersion, reduced to 2% aqueous dispersion after 2 treatments (200 mg/kg/d reduced to 40 mg/kg/d), 5 d/wk 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/d), 5 d/wk for 4 weeks. Severe skin irritation. No evidence of systemic toxicity	No data	[9]

Abbreviations: GI, gastrointestinal; NOEL, no-observed-effect level; PEG, polyethylene glycol.

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 4 times a day for 18 months. [44] Hydroperoxides were the primary oxidation products formed.

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

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

Summary

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

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

The PEGs cocamine and related ingredients represent a series of mixtures of mostly tertiary amines that have alkyl groups derived from plant or animal fatty acids and an average number of PEG groups equal to the number in the chemical name. The structures of the smallest members of the group (eg, PEG-2 cocamine) may have 2 *N*-hydroxyethyl groups, rather than *N*-polyethoxyl groups, or 1 hydrogen atom and 1 *N*-polyethoxyl group. The possibility of similar structural variations is notable for PEG-3, PEG-4, and PEG-5 cocamine and related ingredients. Each PEGs cocamine ingredient is a mixture of compounds, with the fatty acid derived chain lengths ranging from about C6 to C20.

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

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

The VCRP and industry survey data obtained in 2015 and 2014, respectively, indicate that 10 of the ingredients included in this report are used in cosmetic formulations. Polyethylene glycol 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. Polyethylene glycol 2 oleamine has the second greatest number of uses, with a total of 254 uses in rinse-off hair coloring preparations. The highest maximum use concentration for PEG-2 oleamine was 3.5%. Some of the ingredients are reported to be used in body and hand sprays and powder products and could possibly be inhaled. There were 37 PEGs cocamine ingredients that do not appear to be in use. Absorption and metabolism data were not available for the PEGs cocamine ingredients.

The oral LD_{50} of PEG-15 cocamine in rats was 1.2 g/kg, and the LD_{50} of PEG-2 cocamine ranged from 0.75 to 1.3 g/kg. Polyethylene glycol 2 cocamine was classified as a moderate cutaneous irritant, and PEG-15 cocamine was considered a mild irritant. The 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 participants. In another HRIPT, an adult sunscreen formulation containing 2.9% PEG-15 cocamine was not sensitizing in 201 participants. Summary data from a photoallergy study (116 participants) and a phototoxicity study (22 participants) 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).

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

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

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

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

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

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

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

There are substantial differences in physicochemical properties across the PEGs cocamine SOIs and their corresponding analogs. These differences would undoubtedly affect bioavailability in a manner dependent upon the route of exposure.

Another noteworthy difference among the SOIs and analogs is that some of them have *N*-hydroxyethyl side chains and others have polyethoxyl side chains. However, the ether linkage is isosteric with a $–CH_2–$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.

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

The metabolism of the polyethoxylate groups in PEGs cocamine is anticipated to be similar to the metabolism of PEGs. The PEGs are excreted mainly unchanged in the urine and feces after oral or intravenous exposure. None of the final metabolites of 1 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 4 PEGs cocamine selected as SOIs can be summarized as follows.

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

Analogs derived from tallow amine comprise the majority of the identified analogs with repeated-dose toxicity data. These analogs are characterized by greater degrees of unsaturation, compared with the PEGs cocamine.

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

Both in vitro and in vivo genotoxicity studies have been conducted with tallow amine analogs. The results consistently showed an overall lack of genotoxicity across assays and analogs. There were no structural alerts for genotoxicity, and PEG-4 cocamine was predicted to be nonmutagenic and to not be a precursor of chromosomal aberrations using computational methods. The overall negative results of genotoxicity tests and computational predictions are consistent with the data reported for more than 60 genotoxicity tests on more than 30 FND amines and FND amides. Only the in vitro chromosomal 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 software indicated that this ingredient has the

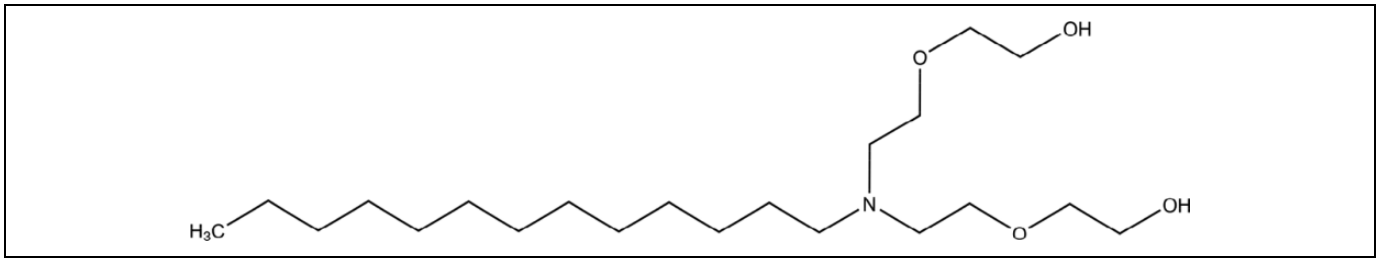


Figure 20. Structure of polyethylene glycol (PEG)-4 cocamine evaluated for genotoxicity and sensitization using computational models.

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

Discussion

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

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

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

Although no sensitization studies were found or submitted for PEG-2 cocamine, 1 negative test on PEG-2 oleamine and 2 studies on PEG-2 tallow amine addressed this end point. The studies on PEG-2 tallow amine included a negative test for delayed contact hypersensitivity in guinea pigs and an apparently positive LLNA in mice (EC3 $<0.1\%$). The Panel noted that the equivocal results of the LLNA for dermal sensitization of PEG-2 tallow amine were confounded by the irritant properties of the ingredient and were inconsistent with the results of the guinea pig test. A quantitative SAR analysis of a representative PEG-4 cocamine structure predicted that PEG-4 cocamine has the potential to be a weak sensitizer, because of potential formation of hydroperoxides by autoxidation of the ethoxylate chains. However, the Panel found that exposure durations and frequencies for the smaller ingredients in this group (ie, PEG-2, PEG-3, PEG-4, and PEG-5 cocamine and related ingredients) would be relatively low, because these ingredients are used predominantly in rinse-off hair coloring products. Thus, sensitization from the use of cosmetic products containing these ingredients is not a likely concern.

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

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

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

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

Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in PEGs cocamine and related ingredients before blending them into cosmetic formulations.

Plants are the source of the fatty acids used to manufacture some of the ingredients of this report. These ingredients are not expected to contain residual pesticides or heavy metals because the production of the ingredients involves significant processing. However, the Expert Panel stressed that the cosmetics industry should continue to use current good manufacturing practices 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 $\leq$15 ppb as corresponding to "negative" aflatoxin content.

The 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% to 99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure to the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

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

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

Conclusion

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

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

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation

is that they would be used in product categories and at concentrations comparable to others in this group.

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

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Author Contributions

I. J. Boyer contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted the manuscript, and critically revised the manuscript. C. Burnett contributed to conception and design, contributed to acquisition, analysis, and interpretation, and drafted the manuscript. B. Heldreth contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. W. Bergfeld, D. Belsito, R. Hill, C. Klaassen, D. Liebler, J. Marks, R. Shank, T. Slaga, P. Snyder, and F. A. Andersen contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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References

1. Nikitakis J, Breslawec HP. *International Cosmetic Ingredient Dictionary and Handbook. 15 ed*. Washington, DC: Personal Care Products Council; 2014.
2. Lanigan RS. Final report on the safety assessment of PEG-2, -3, -5, -10, -15, and -20 Cocamine. *Int J Toxicol*. 1999;18(suppl 1): 43-50.
3. Wu S, Blackburn K, Amburgey J, Jaworska J, Federle T. A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. *Regul Toxicol Pharmacol*. 2010;56(1): 67-81. PM:19770017.
4. CIR Science and Support Committee of the Personal Care Products Council. Information in support of CIR Insufficient Data Ingredients, PEG Cocamines. Unpublished data submitted by the Personal Care Products Council. [Synonyms used: PEG-2 tallow amine = 2,2'-iminobis-,*N*-tallow alkyl derivatives; PEG-20 tallow amine = $(POE)_{20}$ tallow amine]. 2011:62.
5. CIR Science and Support Committee of the Personal Care Products Council. PEG Cocamines and Structurally Related Ingredients: A Structure-Activity Relationship (SAR) Approach to Address the Data Gaps Identified by the CIR Expert Panel. Unpublished data submitted by Personal Care Products Council. [Synonyms used: PEG-2 tallow amine = 2,2'-iminobis-,*N*-tallow alkyl derivatives; PEG-20 tallow amine = $(POE)_{20}$ tallow amine or polyethoxylated tallow amine]. 2012:40.
6. Blackburn K, Wu S. A structure activity relationship (SAR) based case study for a cosmetic ingredient. Paper presented at: 122nd CIR Expert Panel Meeting; March 5, 2012.
7. Skare JA, Blackburn K, Wy S, et al. Use of read-across and computer-based predictive analysis for the safety of PEG cocamines. *Regul Toxicol Pharmacol*. 2015;71(3):515-528.
8. Personal Care Products Council. More information: PEG Cocamine and Related Ingredients. Unpublished data submitted by the Personal Care Products Council. 2011:46.
9. Toxicology—Regulatory Services, Inc. FND Ether Amines Category HPV Chemicals Challenge—Appendix A Robust Summaries for Reliable Studies. 2003. Report No. 201-14978. A-1-A-614. Prepared for the American Chemistry Council's Fatty Nitrogen Derivatives Panel Amines Task Group [Synonyms used: PEG-2 tallow amine = 2,2'-iminobis-,*N*-tallow alkyl derivatives or tallow bis(2-hydroxyehtyl amine); PEG-8 stearamine = alkylamineethoxylate; PEG-20 tallow amine = ethanol,2,2'-iminobis-,*N*-tallow alkyl derivatives, $(POE)_{20}$ tallow amine, or polyethoxylated tallow amine; PEG-50 stearamine = polyoxyethylene octadecylamine].
10. US Environmental Protection Agency (USEPA) Office of Prevention, Pesticides and Toxic Substances. Alkyl Amine Polyethoxylates (JITF CST 4 Inert Ingredients); Human Health Risk Assessment to Support Proposed Exemption from Requirement of a Tolerance When Used as Inert Ingredients in Pesticide Formulations. 2009; 1-94. [Synonyms used: PEG-2 cocamine = coco, POE n=2; POE-5/POP-12 tallow amine = tallow, POE n=5/12; PEG-15 tallow amine = tallow, POE n+15].
11. EG&G Mason Research Institute. Salmonella/mammalian microsome mutagenesis assay (Ames test). 1981. Report No. 003-407-637-1.
12. Hazelton Laboratories Europe, Ltd. A 4 week percutaneous toxicity study in the rabbit. 1981. Report No. ECM BTS 306 ET Base.
13. Hazelton Laboratories Europe, Ltd. 13 week oral (dietary) toxicity study in the rat. 1982. Report No. ECM BTS, E1095.01.
14. Boyer IJ. Notation based on the discussions of the CIR Expert Panel at the 8-9 Decmeber 2014 Panel meeting. 2015.
15. Salunkhe DK, Chavan JK, Adsule RN, Kadam SS. *World Oilseeds: Chemistry, Technology, and Utilization*. New York, NY: Van Nostrand Reinhold; 1992.
16. Anon. Final report on the safety assessment of polyethylene glycols (PEGs) -6, -8, -32, -75, -150, -14M, -20M. *J Am Coll Toxicol*. 1993;12(5):429-457.
17. Jeen Products. Surfactants—JEETOX C-2 (PEG-2 Cocamine). http://www.jeen.com/technical/JEETOX%20C-2%20SPEC.pdf. Jeen Products. Updated April 24, 2014. Accessed February 1, 2015.
18. Andersen FA, Belsito DV, Hill RA, et al. Final report of the cosmetic ingredient review expert panel: amended safety

assessment of triethylene glycol and polyethylene glycols (PEGs)-4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEGs = 4 as used in Cosmetics. 2010:1-49.

19. Personal Care Products Council. Composition PEG-2 and PEG-5 Cocamine. *Unpublished data submitted by the Personal Care Products Council*. 2015.
20. Personal Care Products Council. Concentration of Use by FDA Product Category PEG-2 Cocamine, PEG-3 Cocamine, PEG-4 Cocamine, PEG-5 Cocamine, PEG-8 Cocamine, PEG-10 Cocamine, PEG-12 Cocamine, PEG-15 Cocamine, PEG-20 Cocamine, PEG-2 Oleamine, PEG-5 Oleamine, PEG-6 Oleamine, PEG-10 Oleamine, PEG-15 Oleamine, PEG-20 Oleamine, PEG-25 Oleamine, PEG-30 Oleamine, PEG-2 Tallow Amine, PEG-7 Tallow Amine, PEG-11 Tallow Amine, PEG-15 Tallow Amine, PEG-20 Tallow Amine, PEG-22 Tallow Amine, PEG-25 Tallow Amine, PEG-30 Tallow Amine. Unpublished data submitted by the Personal Care Products Council. 2010.
21. Personal Care Products Council. Concentration of Use by FDA Product Category: PEG Cocamines and Related Ingredients. *Unpublished data submitted by Personal Care Products Council. October* 3, 2014.
22. Johnsen MA. The influence of particle size. *Spray Technol Market*. 2004;14(11):24-27.
23. Rothe H. Special aspects of cosmetic spray evalulation. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, DC; 2011.
24. Bremmer HJ, Prud'Homme de Lodder LCH, Engelen JGM. Cosmetics Fact Sheet: To Assess the Risks for the Consumer; Updated Version for ConsExpo 4. 2006. Report No. RIVM 320104001/2006. 1-77.
25. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.
26. Bradberry SM, Proudfoot AT, Vale JA. Glyphosate poisoning. *Toxicol Rev*. 2004;23(3):159-167. PM:15862083.
27. Williams GM, Kroes R, Munro IC. Safety evaluation and risk assessment of the herbicide roundup and its active ingredient, glyphosate, for humans. *Regul Toxicol Pharmacol*. 2000; 31(2 pt 1):117-165. PM:10854122.
28. US Environmental Protection Agency. Pesticide inert ingredient: polyoxyethylene tallow amine. http://iaspub.epa.gov/apex/pesticides/f?p=INERTFINDER:3:0::NO::P3_ID:6708. Updated February 9, 2015. Accessed February 9, 2015.
29. Personal Care Products Council. Requested Studies to Support the Safety of PEG Cocamine Ingedients. Unpublished data submitted by Personal Care Products Council. 2014.
30. European Chemicals Agency. Information on chemicals—2,2'-(C16-18 (evennumbered, C18 unsaturated) alkyl imino) diethanol. http://echa.europa.eu/information-on-chemicals. Updated 2015. Accessed April 29, 2015.
31. Personal Care Products Council. Summaries of Sensitization Studies PEG-2 Tallow Amine. Summary of a delayed contact hypersensitivity study in guinea pigs, Hill Top, 1978, and a local lymph node assay in mice, MB Laoratories, 2002, of PEG-2 Tallow Amine submitted by the Personal Care Products Council. 2015.
32. TKL Research, Inc. Repeated Insult Patch Study of a Leave-on Hair Styling Product Containing 1% PEG-15 Cocamine. Study No. A01393.01. Unpublished data submitted by the Personal Care Products Council. 2002.
33. TKL Research, Inc. Study Summary: HRIPT with Adult Sun Screen formulation Containing 2.9% PEG-15 Cocamine. TKL Research, Inc; 2009.
34. Anonymous. Forearm open application patch test of a hair dye formulation containing 3.4% PEG-5 Soyamine. 2007.
35. Personal Care Products Council. PEG-5 Soyamine. Unpublished data submitted by the Personal Care Products Council. 2015.
36. Blackburn K, Bjerke D, Daston G, et al. Case studies to test: a framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. *Regul Toxicol Pharmacol*. 2011;60(1):120-135. PM:21420459.
37. Wu S, Fisher J, Naciff J, et al. Framework for identifying chemicals with structural features associated with the potential to act as developmental or reproductive toxicants. *Chem Res Toxicol*. 2013;26(12):1840-1861. PM:24206190.
38. Fruijtier-Polloth C. Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products. *Toxicology*. 2005;214(1-2):1-38. PM:16011869.
39. Webster R, Didier E, Harris P, et al. PEGylated proteins: evaluation of their safety in the absence of definitive metabolism studies. *Drug Metab Dispos*. 2007;35(1):9-16. PM:17020954.
40. Chatman LA, Morton D, Johnson TO, Anway SD. A strategy for risk management of drug-induced phospholipidosis. *Toxicol Pathol*. 2009;37(7):997-1005. PM:20008549.
41. Toxicology—Regulatory Services, Inc. Fatty Nitrogen Derived Amines Category High Production Volume (HPV) chemical challenge: Assessment of data availability and test plan. December 29, 2003. Report No. 201-14978. 1-40. Prepared for the American Chemistry Council's Fatty Nitrogen Derivatives Panel Amines Task Group.
42. Firriolo JM, Morris CF, Trimmer GW, Twitty LD, Smith JH, Freeman JJ. Comparative 90-day feeding study with low-viscosity white mineral oil in Fischer-344 and Sprague-Dawley-derived CRL:CD rats. *Toxicol Pathol*. 1995;23(1):26-33. PM: 7770697.
43. Shoda T, Toyoda K, Uneyama C, Takada K, Takahashi M. Lack of carcinogenicity of medium-viscosity liquid paraffin given in the diet to F344 rats. *Food Chem Toxicol*. 1997;35(12): 1181-1190. PM:9449224.
44. Bodin A, Linnerborg M, Nilsson JL, Karlberg AT. Novel hydroperoxides as primary autoxidation products of a model ethoxylated surfactant. *J Surfactants Deterg*. 2002;5(2):107-110.
45. Burnett C, Fiume M, Bergfeld, et al. *Final Report: Plant-Derived Fatty Acid Oils as Used in Cosmetics*. Washington, DC: Cosmetic Ingredient Review; 2011:1-100.
46. Personal Care Products Council. Analytical Information on the PEG-2 Tallow Amine Tested in the Oral Toxicology Study in

Rats Submitted October 31, 2014. Unpublished data submited by the Personal Care Products Council. December 18, 2014.
47. Andersen FA, Belsito DV, Hill RA, et al. Final report of the cosmetic ingredient review expert panel: amended safety assessment of triethylene glycol and polyethylene glycols (PEGs)-4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEGs > or = 4 as used in Cosmetics. 2010. 1-49.
48. Anon. Final report on the safety assessment of triethylene glycol and PEG-4. *Int J Toxicol*. 2006;25(suppl 2):121-138.
49. Cosmetic Ingredient Review. Final report on the safety assessment of lauramine and stearamine. *J Am Coll Toxicol*. 1995;14(3): 196-203.
50. Burnett CL, Bergfeld WF, Belsito DV, et al. Final report on the safety assesment of *Cocos nucifera* (coconut) oil and related ingredients. *Int J Toxicol*. 2011;30(3 suppl):5S-16S.
51. Elder RL. Final report on the safety assessment of coconut oil, coconut acid, hydrogenated coconut acid, and hydrogenated coconut oil. *J Am Coll Toxicol*. 1986;50(3):103-121.
52. Cosmetic Ingredient Review. Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid and stearic acid. *J Am Coll Toxicol*. 1987;6(3):321-401.
53. Cosmetic Ingredient Review. Annual review of cosmetic ingredeint safety assessments - 2004/2005. *Int J Toxicol*. 2006;25(2): 1-89.
54. Cosmetic Ingredient Review. Final report on the safety assessment of tallow, tallow glyceride, tallow glycerides, hydrogented tallow glyceride, and hydrogenated tallow glycerides. *J Am Coll Toxicol*. 1990;9(2):153-164.
55. Cosmetic Ingredient Review. Annual review of cosmetic ingredient safety assessments: 2005/2006. *J Am Coll Toxicol*. 2008; 27(suppl 1):77-142.
56. Personal Care Products Council. Tertiary Amine Content of PEG Fatty Acid Amine Ingredients. Unpublished data submitted by the Parsonal Care Products Council. 2015.
57. Jeen Products. *Surfactants—JEETOX C-5 (PEG-5 Cocamine)*. http://www.jeen.com/technical/JEETOX%20C-5%20SPEC.pdf. Fairfield, NJ. Updated December 10, 2014.
58. AkzoNobel Surface Chemistry. *Polyoxyethylene (5) Cocoalkylamines—Ethomeen C/15 (PEG-5 Cocamine)*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8652_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
59. Jeen Products. *Surfactants—JEETOX C-15 (PEG-15 Cocamine)*. http://www.jeen.com/technical/JEETOC%20C-15%20SPEC.pdf. Fairfield, NJ. Updated April 24, 2014. Accessed February 1, 2015.
60. Jeen Products. *Surfactants—JEETOX T-2 (PEG-2 Tallow Amine)*. http://www.jeen.com/technical/JEETOX%20T-2%20SPEC.pdf. Fairfield, NJ. Updated April 25, 2014. Accessed February 1, 2015.
61. AkzoNobel Surface Chemistry. *Bis(2-hydroxyethyl) Tallowalkylamines—Ethomeen T/12 (PEG-2 Tallow Amine)*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8660_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
62. Jeen Products. *Surfactants—JEETOX T-5 (PEG-5 Tallow Amine)*. http://www.jeen.com/technical/JEETOX%20T-5%20SPEC.pdf. Fairfield, NJ. Updated April 10, 2011. Accessed February 1, 2015.
63. AkzoNobel Surface Chemistry. *Tallow Amine Ethoxylates—Ethomeen T/15 (PEG-5 Tallow Amine) NA*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8661_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
64. AkzoNobel Surface Chemistry. *Tallow Amine Ethoxylates—Ethomeen T/15 (PEG-5 Hydrogenated Tallow Amine) NA*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8661_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
65. AkzoNobel Surface Chemistry. *Tallow Amine Ethoxylates—Ethomeen T/15 (PEG-5 Hydrogenated Tallow Amine) AF, EU*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8297_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
66. Jeen Products. *Surfactants—JEETOX T-15 (PEG-15 Tallow Amine)*. http://www.jeen.com/technical/JEETOX%20T-15%20SPEC.pdf. Fairfield, NJ. Updated April 24, 2014. Accessed February 1, 2015.
67. AkzoNobel Surface Chemistry. *Polyoxyethylene (15) Tallowalkylamines—Ethomeen T/25 (PEG-15 Tallow Amine)*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8662_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
68. AkzoNobel Surface Chemistry. *Hydrogenated Tallow Amine Ethoxylate—Ethomeen HT/12 (PEG-2 Hydrogenated Tallow Amine)*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8427_PDS.pdf. Chicago, IL. Updated January 22, 2014. Accessed February 2, 2015.
69. AkzoNobel Surface Chemistry. *Polyoxyethylene (5) Soyaalkylamines—Ethomeen SV/15 (PEG-5 Soyamine)*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_10200_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
70. AkzoNobel Surface Chemistry. *Polyoxyethylene (15) Soyaalkylamines—Ethomeen SV/25 (PEG-15 Soyamine)*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_10201_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
71. Jeen Products. *Surfactants—JEETOX HTA-5 (PEG-5 Stearamine)*. http://www.jeen.com/technical/JEETOX%20H-5%20SPEC.pdf. Fairfield, NJ. Updated April 24, 2014. Accessed February 1, 2015.
72. AkzoNobel Surface Chemistry. *Bis(2-hydroxyethyl) Octadecylamine—Ethomeen 18/12 (PEG-5 Stearamine)*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8667_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015.
73. AkzoNobel Surface Chemistry. *Polyoxyethylene (15) octadecylamine—Ethomeen 18/25 (PEG-15 Stearamine)*. http://sc.akzonobel.com/ProductDocuments/AkzoNobel_8668_PDS.pdf. Chicago, IL. Updated January 17, 2014. Accessed February 1, 2015
74. Food and Drug Administration. *Frequency of Use of Cosmetic Ingredients*. College Park, MD: FDA Database; 2015.