
Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics

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All interested persons are provided 60 days from the above release date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The 2018 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

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INTRODUCTION

This scientific literature review is the initial step in preparing a safety assessment of the alkoxylated fatty amides. The 41 alkoxylated fatty amides reviewed herein are listed in Table 1. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all but a few of these ingredients are reported to function in cosmetics as a surfactant – emulsifying agent (Table 2).¹

The rationale for this grouping of ingredients stems from the fact that the ingredients in this report are each structurally related as alkoxylated simple amides. Although a few of the ingredients in this report (e.g., PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA) are di-*N,N*-alkoxyl-substituted amides (and similar to the amines in the Cosmetic Ingredient Review (CIR) PEGs Cocamine report; ingredients reviewed in that report were found safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating²), most of these alkoxylated fatty amides are mono-*N*-alkoxyl-substituted. These ingredients are classic surfactants, with a hydrophobic, fatty alkyl tail on one end and a hydrophilic, alkoxyated head group on the other end.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

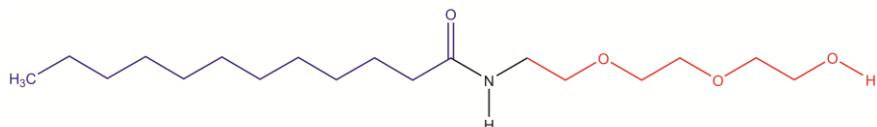
Much of the data included in this safety assessment was obtained from Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) hazard assessments.³⁻⁵ These data summaries are available on the NICNAS website, and when deemed appropriate, information from the summaries has been included in this report.

CHEMISTRY

Definition and Structure

The definitions and structures of the alkoxylated fatty amides included in this review are provided in Table 2.

These ingredients are alkoxylated simple amides, and most of these alkoxylated fatty amides are mono-*N*-alkoxyl-substituted. However, a few of the ingredients (such as PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA) are di-*N,N*-alkoxyl-substituted amides. The ingredients reviewed in this report are classic surfactants, with a hydrophobic fatty alkyl tail on one end and a hydrophilic alkoxylated head group on the other end (Figure 1).



PEG-3 Lauramide

Figure 1. Example of a fatty acid amide, and its alkoxylated surfactant structure

Physical and Chemical Properties

Physical and chemical properties of PEG-6 Cocamide, PEG-4 Rapeseedamide, and PPG-2 Hydroxyethyl Cocamide are described in Table 3.

Method of Manufacture

Methods of manufacture were not discovered in the published literature, and unpublished data were not submitted.

Impurities

PEG-4 Rapeseedamide

A supplier reports that PEG-4 Rapeseedamide is 92 - 93% "active matter,"⁶ specifications for the presence of 1,4-dioxane are 1 ppm maximum.⁷ According to another source, PEG-4 Rapeseedamide (as the raw material) is reported to be 60-80% pure. Low levels of 1,4-dioxane, "down to 100 mg/kg or 100 mg/l," may be present. Other possible impurities were not specified, but based on the structure, "it is not expected to contain hazardous nitrosamine impurities."

USE
Cosmetic

The safety of the cosmetic ingredients addressed in this safety assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. VCRP data obtained from the FDA in 2018⁸ and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council) in 2015⁹ indicate that 11 of the 41 ingredients included in this safety assessment are used in cosmetic formulations.

According to 2018 VCRP survey data, PPG-2 Hydroxyethyl Cocamide is reported to be used in 342 formulations, and PEG-4 Rapeseedamide is reported to be used in 280 formulations (Table 4).⁸ All other in-use ingredients are reported to be used in less than 30 formulations. The results of the concentration of use survey conducted by the Council in 2015 indicate PEG-4 Rapeseedamide has the highest concentration of use, at 9.3% in hair dyes and colors.⁹ The ingredient with the next highest reported concentration of use is PPG-2 Hydroxyethyl Cocamide; it is used at 7.5% in “other” non-coloring hair preparations.

The alkoxylated fatty amides are primarily used in rinse-off formulations, with few uses reported in leave-on formulations. Most of the reported uses are in some type of hair or cleansing formulation. However, there are some uses that result in leave-on dermal exposure; the highest concentration of use reported for products resulting in leave-on dermal exposure is 3% PPG-2 Hydroxyethyl Cocamide in body and hand products.⁹

Use concentration data were reported for PEG-6 Lauramide and PEG-50 Tallow Amide in response to the Council survey, but no uses were received in the VCRP; it should be presumed there is at least one use in every category for which a use concentration is reported. Additionally, uses were reported in the VCRP for PEG-3 Cocamide and PEG-5 Cocamide, but no concentrations of use were reported for these ingredients in the industry survey. The ingredients not in use, according to 2018 VCRP data and the industry survey, are listed in

Table 5.

The majority of the in-use alkoxylated fatty amides have uses that result in contact with the mucous membranes; for example, PEG-6 Lauramide and PPG-2 Cocamide are used in bath soaps and detergents at up to 4%.⁹ According to the Council survey, PPG-2 Cocamide is used in aerosol hair spray formulations at a maximum concentration of 0.8%, and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.^{10,11} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{12,13}

The alkoxylated fatty amides are not restricted from use in any way under the rules governing cosmetic products in the European Union.¹⁴

Non-Cosmetic

PEG-4 Rapeseedamide is used in industrial dishwashing and laundry care.¹⁵

TOXICOKINETICS

Toxicokinetics data (such as dermal penetration and absorption, distribution, metabolism, and excretion data) were not discovered in the published literature, and unpublished data were not submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute toxicity studies summarized below³⁻⁵ are described in Table 6.

The dermal LD₅₀s of PEG-4 Rapeseedamide (60-80% pure) and PPG-2 Hydroxyethyl Cocamide in Sprague-Dawley rats were > 2000 mg/kg. In rats, the oral LD₅₀s of PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across) were > 2000 mg/kg. In both the dermal and the orals studies, this was the highest dose tested. In inhalation studies of PEG-4 Rapeseedamide (60 - 80%

pure), groups of two Wistar rats were exposed to 4.92 mg/l (actual concentration) of the test article for 0.5 - 4 h, and groups of six Wistar rats were exposed to 6 mg/l (actual concentration) of the test article for 4 h, via oronasal exposure. Some deaths were reported in the first, but not the second study, and the LC₅₀s were reported to be 1-5 mg/L/4 h and 6 mg/L/4 h, respectively.

Short-Term Toxicity Studies

Oral

PEG-4 Rapeseedamide

Groups of 5 male and 5 female Sprague-Dawley rats were dosed by gavage with 0, 15, 150, or 1000 mg/kg bw/day (PEG-4 Rapeseedamide 60 - 80% pure) in arachis oil for 28 days, in accord with Organisation for Economic Co-operation and Development test guideline (OECD TG) 407.³ All animals survived until study termination. A statistically significant decrease in body weights was observed in females of the mid-dose group during wk 2; a non-statistically significant reduction in body weight gain and food consumption, when compared with controls, was reported for males of the high-dose group. No treatment related behavioral, functional performance, or sensory reactivity changes were observed. No toxicologically-significant changes in clinical chemistry, hematology, or urinalysis parameters were reported. A statistically significant, non-dose dependent, reduction in absolute thymus weights was observed in low- and high-dose males. Microscopic forestomach lesions (acanthosis and hyperkeratosis, occasionally with associated subepithelial inflammatory cell infiltrates) in high dose males were attributed to slight irritancy of the test material, and cortical hypertrophy of the adrenal glands observed in 3 females in the high dose group may reflect a non-specific stress response to the irritancy of the test material. The no-observable-adverse-effect-levels (NOAELs) were 15 and 150 mg/kg bw/day for male and female rats, respectively.

PPG-2 Hydroxyethyl Cocamide

Groups of 3 male and 3 female albino rats were dosed with 0, 100, 500, or 1000 mg/kg/day PPG-2 Hydroxyethyl Cocamide by gavage for 7 days, in accord with OECD TG 407.⁴ The vehicle was not specified. All animals survived until study termination. Transient salivation noted with the highest doses was considered unremarkable. There were no effects on kidney, liver, or spleen weights. No gross lesions were observed at necropsy. Clinical chemistry, hematology, and microscopic studies were not conducted. No evidence of toxicity was observed.

In a 28-day study conducted in accord with OECD TG 407, groups of 5 male and 5 female albino rats were dosed by gavage with 0, 15, 150, or 1000 mg/kg/day PPG-2 Hydroxyethyl Cocamide for 28 days.⁴ The vehicle was not specified. No mortalities were reported. Transient post-dosing salivation was observed in some animals of all test groups. No treatment-related changes were reported for clinical chemistry or hematology parameters. Changes in urinary parameters included a decrease in urine volume and in urinary phosphorus and an increase in urinary pH in high-dose males, and a decrease in urinary potassium in high-dose males and high- and mid-dose females; these changes were not supported by pathological changes. Slight decreases in absolute and relative thymus weights were not considered to be toxicologically significant. Focal basophilic cortical tubules observed in three high dose male rats were not considered treatment-related. The no-observable-effect-level (NOEL) was 15 mg/kg/day, and the NOAEL was 1000 mg/kg/day.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

PEG-4 Rapeseedamide

A reproductive/developmental toxicity screening test was performed in accord with OECD TG 421 using groups of 10 male and 10 female rats that were dosed with 0, 15, 15, or 500 mg/kg bw/day PEG-4 Rapeseedamide (60 - 80% pure) in arachis oil by gavage for 55 days.³ Animals were paired for mating on day 15 of dosing. Males were killed on day 43; females were allowed to litter, and were killed on 5 days post-partum. No mortalities were reported. No adverse effects on parental body weights, mating performance, fertility, or length of gestation were reported, and there were no effects on litter size, total litter weights, sex ratio, or viability of offspring. The NOAEL was 500 mg/kg bw/day.

GENOTOXICITY STUDIES

The genotoxicity studies summarized below³⁻⁵ are also described in Table 7.

PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across) were not mutagenic in Ames tests at concentrations up to 5000 µg/plate, with or without metabolic activation. In mammalian chromosomal aberration studies, PEG-4 Rapeseedamide (60 - 80% pure) was not clastogenic at up to 5000 µg/ml, with or without metabolic activation, and PPG-2 Hydroxyethyl Cocamide was not clastogenic at concentrations up to 250 µg/ml without metabolic activation. PPG-2 Hydroxyethyl Cocamide was "not likely to be clastogenic" with metabolic activation; a statistically significant increase in the proportion of metaphase figures with chromosomal aberrations was reported at 450 and 500 µg/ml (concentrations that were cytotoxic).

In the mouse micronucleus test, PEG-4 Rapeseedamide (60 - 80% pure) dosed orally at \leq 400 mg/kg bw in arachis oil³ and aq. PPG-2 Hydroxyethyl Cocamide dosed intraperitoneally at \leq 1000 mg/kg were not clastogenic.⁴ Additionally, in Sprague-Dawley rats, dosing with up to 2000 mg/kg aq. PPG-2 Hydroxyethyl Cocamide by gavage did not induce DNA damage.

CARCINOGENICITY STUDIES

Carcinogenicity studies were not discovered in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below^{3,4} are also described in Table 8.

Undiluted PEG-4 Rapeseedamide (60 - 80% pure) was irritating, but not corrosive, to rabbit skin; duration of dosing was not specified. Application of undiluted PPG-2 Hydroxyethyl Cocamide to rabbit skin for 4 h produced thickening of the skin, desquamation, and well-defined erythema; 3 min and 1 h exposure were not irritating. In Magnusson-Kligman maximization studies in guinea pigs, PEG-4 Rapeseedamide (60 - 80% pure; intradermal induction 0.2%, topical induction – 10%, topical challenge – 0.01%; in sesame oil) and PPG-2 Hydroxyethyl Cocamide (intradermal induction – 0.5%, topical induction – 50%, topical challenge – 5 and 10%; in water) were not sensitizers.

In clinical testing, 0.5% aq. PEG-4 Rapeseedamide (60 - 80% pure) was not a sensitizer in a human repeated insult patch test (HRIFT), and 5% aq. PPG-2 Hydroxyethyl Cocamide was not an irritant. Both studies were performed using 50 subjects.

OCULAR IRRITATION STUDIES

PEG-4 Rapeseedamide

The ocular irritation potential of PEG-4 Rapeseedamide (60 - 80% pure) was evaluated in three New Zealand White rabbits in an acute eye irritation/corrosion test (OECD TG 405).³ The undiluted test material was instilled into the conjunctival sac of one eye of each animal, and the eyes were observed for 7 days. (The volume instilled was not specified.) The test material was slightly irritating to rabbit eyes. The mean scores (calculated using the 24, 48, and 72 h scores for each animal) for the conjunctiva ranged from 1.3-1.7/2 for redness; 0-0.7/1 for chemosis; and 0.3/1 for discharge; irritation resolved within 7 days. Corneal opacity and iridal inflammation were not observed.

PPG-2 Hydroxyethyl Cocamide

Three male New Zealand White rabbits were used to determine the ocular irritation potential of PPG-2 Hydroxyethyl Cocamide.⁴ One-tenth (0.1) ml of the test article was instilled into the conjunctival sac of one eye of each rabbit, and the eyes were not rinsed. The contralateral eye served as an untreated control. PPG-2 Hydroxyethyl Cocamide was moderately irritating. Corneal opacification was observed in all animals at 24 h. Diffuse red coloration of the conjunctiva with eyelid swelling was reported for up to 7 days, and iridal inflammation was observed in one animal at day 14.

CLINICAL STUDIES

Case Reports

PEG-4 Rapeseedamide

A female patient developed dermatitis 1 month after exposure to massage oils while working as a masseuse, and presented with eczema on the flexor wrist and forearm of 4 mos duration.¹⁶ Patch testing was conducted using a standard series and with oils from work. Two massage oils from the same manufacturer produced positive reactions. Subsequent testing with components of those oils resulted in positive reactions to 3.0% PEG-4 Rapeseedamide. Positive reactions were also reported in a dilution series with PEG-4 Rapeseedamide; “+++” reactions were observed with 0.003 - 3.0% in petrolatum and 0.03 - 3% aq., and a + reaction was observed with 0.003% aq. PEG-4 Rapeseedamide. Control subjects (n = 28) did not react to 0.3% PEG-4 Rapeseedamide in petrolatum.

SUMMARY

This assessment reviews the safety of 41 alkoxylated fatty amides as used in cosmetics. These ingredients are alkoxylated simple amides, and most of these alkoxylated fatty amides are mono-*N*-alkoxyl-substituted. However, a few of the ingredients (such as PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA) are di-*N,N*-alkoxyl-substituted amides. The ingredients reviewed in this report are classic surfactants, with a hydrophobic fatty alkyl tail on one end and a hydrophilic alkoxylated head group on the other end.

Eleven of the 41 ingredients included in this assessment are reported to be in use. PPG-2 Hydroxyethyl Cocamide has the greatest reported frequency of use (342 formulations), and PEG-4 Rapeseedamide has the second greatest reported number of uses (280). The alkoxylated fatty amides are primarily used in rinse-off formulations, and most of the reported uses are in

some type of hair or cleansing formulation. PEG-4 Rapeseedamide has the highest concentration of use, at 9.3% in hair dyes and colors. PPG-2 Hydroxyethyl Cocamide has the next highest reported concentration of use is; it is used at 7.5% in “other” non-coloring hair preparations. There are some uses that result in leave-on dermal exposure; the highest concentration of use reported for products resulting in leave-on dermal exposure is 3% PPG-2 Hydroxyethyl Cocamide in body and hand products. The majority of the in-use alkoxylated fatty amides have uses that result in contact with the mucous membranes; for example, PEG-6 Lauramide and PPG-2 Cocamide are used in bath soaps and detergents at up to 4%. According to the Council survey, PPG-2 Cocamide is used in aerosol hair spray formulations at a maximum concentration of 0.8%, and could possibly be inhaled.

The dermal LD₅₀s of PEG-4 Rapeseedamide (60 - 80% pure) and PPG-2 Hydroxyethyl Cocamide in Sprague-Dawley rats were > 2000 mg/kg. In rats, the oral LD₅₀s of PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across) were > 2000 mg/kg. In both the dermal and the orals studies, this was the highest dose tested. In inhalation studies of PEG-4 Rapeseedamide (60 - 80% pure), groups of two Wistar rats were exposed to 4.92 mg/l (actual concentration) of the test article for 0.5 - 4 h, and groups of six Wistar rats were exposed to 6 mg/l (actual concentration) of the test article for 4 h, via oronasal exposure. Some deaths were reported in the first, but not the second study, and the LC₅₀s were reported to be 1-5 mg/L/4 h and 6 mg/L/4 h, respectively.

In a 7-day oral study using groups of 6 albino rats, there was no evidence of toxicity with oral administration of ≤ 1000 mg/kg/day PPG-2 Hydroxyethyl Cocamide. In 28-day oral studies using groups of 10 Sprague-Dawley rats, NOAELs of 15 and 150 mg/kg bw/day PEG-4 Rapeseedamide (60 - 80% pure) in arachis oil were reported for male and female rats, respectively, and for PPG-2 Hydroxyethyl Cocamide, the NOEL was 15 mg/kg/day and the NOAEL was 1000 mg/kg/day. The maximum dose administered in both studies was 1000 mg/kg bw/day. With PEG-4 Rapeseedamide, a statistically significant, non-dose dependent, reduction in absolute thymus weights was observed in low and high-dose males; microscopic forestomach lesions in high dose males were attributed to slight irritancy of the test material; and cortical hypertrophy of the adrenal glands, observed in 3 females in the high dose group, may reflect a non-specific stress response to the irritancy of the test material. With PPG-2 Hydroxyethyl Cocamide, slight decreases in absolute and relative thymus weights were not considered to be toxicologically significant, and focal basophilic cortical tubules observed in three high dose male rats were not considered treatment-related.

A reproductive/developmental toxicity screening test was performed with 20 rats that were dosed with up to 500 mg/kg bw/day PEG-4 Rapeseedamide (60-80% pure) in arachis oil by gavage for 55 days. No adverse reproductive effects and no parental toxicity were reported. The NOAEL was 500 mg/kg bw/day.

PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across) were not mutagenic in Ames tests at concentrations up to 5000 µg/plate, with or without metabolic activation. In mammalian chromosomal aberration studies, PEG-4 Rapeseedamide (60 - 80% pure) was not clastogenic at up to 5000 µg/ml, with or without metabolic activation, and PPG-2 Hydroxyethyl Cocamide was not clastogenic at concentrations up to 250 µg/ml without metabolic activation. PPG-2 Hydroxyethyl Cocamide was “not likely to be clastogenic” with metabolic activation; a statistically significant increase in the proportion of metaphase figures with chromosomal aberrations was reported at 450 and 500 µg/ml (concentrations that were cytotoxic). In the mouse micronucleus test, PEG-4 Rapeseedamide (60 - 80% pure) dosed orally at ≤ 400 mg/kg bw in arachis oil and aq. PPG-2 Hydroxyethyl Cocamide dosed intraperitoneally at ≤ 1000 mg/kg were not clastogenic. Additionally, in Sprague-Dawley rats, dosing with up to 2000 mg/kg aq. PPG-2 Hydroxyethyl Cocamide by gavage did not induce DNA damage.

Undiluted PEG-4 Rapeseedamide (60 - 80% pure) was irritating, but not corrosive, to rabbit skin; duration of dosing was not specified. Application of undiluted PPG-2 Hydroxyethyl Cocamide to rabbit skin for 4 h produced thickening of the skin, desquamation, and well-defined erythema; 3 min and 1 h exposure were not irritating. In Magnusson-Kligman maximization studies in guinea pigs, PEG-4 Rapeseedamide (60 - 80% pure; intradermal induction 0.2%, topical induction – 10%, topical challenge – 0.01%; in sesame oil) and PPG-2 Hydroxyethyl Cocamide (intradermal induction – 0.5%, topical induction – 50%, topical challenge – 5 and 10%; in water) were not sensitizers.

In clinical testing, 0.5% aq. PEG-4 Rapeseedamide (60 - 80% pure) was not a sensitizer in a human repeated insult patch test (HRIPT), and 5% aq. PPG-2 Hydroxyethyl Cocamide was not an irritant. Both studies were performed using 50 subjects.

Ocular irritation studies were performed using New Zealand White rabbits. Undiluted PEG-4 Rapeseedamide (60 - 80% pure) was slightly irritating to rabbit eyes, and undiluted PPG-2 Hydroxyethyl Cocamide was moderately irritating.

INFORMATION SOUGHT

The CIR is seeking the following information on all ingredients that comprise the alkoxylated fatty amides family for use in the resulting safety assessment. Specifically, the following would strengthen this safety assessment.

1. Methods of manufacture

2. Impurities data
3. Dermal absorption data; if absorbed, additional data may be requested
4. Dermal irritation and sensitization data
5. Any other data relevant to the determination of safety of these ingredients as used in cosmetics

TABLES

Table 1. Alkoxylated fatty amides included in this safety assessment

PEG-2 Cocamide	PEG-2 Lauramide	PEG-10 Stearamide
PEG-3 Cocamide	PEG-3 Lauramide	PEG-15 Stearamide
PEG-4 Cocamide	PEG-5 Lauramide	PEG-50 Stearamide
PEG-5 Cocamide	PEG-6 Lauramide	PEG-5 Tallow Amide
PEG-6 Cocamide	PEG-11 Lauramide	PEG-8 Tallow Amide
PEG-7 Cocamide	PEG-3 Oleamide	PEG-50 Tallow Amide
PEG-11 Cocamide	PEG-4 Oleamide	PEG-2 Tallowamide DEA
PEG-20 Cocamide	PEG-5 Oleamide	Polyglyceryl-4-PEG-2 Cocamide
PEG-3 Cocamide DEA	PEG-6 Oleamide	PPG-2 Cocamide
PEG-20 Cocamide MEA	PEG-7 Oleamide	PPG-1 Hydroxyethyl Caprylamine
PEG-6 Hydrogenated Palmamide	PEG-9 Oleamide	PPG-2 Hydroxyethyl Cocamide
PEG-50 Hydrogenated Palmamide	PEG-5 Oleamide Dioleate	PPG-2 Hydroxyethyl Coco/Iosostearamide
PEG-13 Hydrogenated Tallow Amide	PEG-4 Rapeseedamide	PPG-3 Hydroxyethyl Soyamide
PEG-5 Lanolinamide	PEG-4 Stearamide	

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment. ¹ CIR Staff

Ingredient CAS No.	Definition & Structure	Function(s)
<i>Ethoxylated</i>	<i>General formula:</i>	
PEG-2 Cocamide [61791-08-0 (generic to PEG-x Cocamides)]	PEG-2 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 2.	surfactant - emulsifying agent; surfactant - foam booster
PEG-3 Cocamide 61791-08-0 (generic)	PEG-3 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster
PEG-4 Cocamide [61791-08-0 (generic to PEG-x Cocamides)]	PEG-4 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 4.	surfactant - emulsifying agent
PEG-5 Cocamide 61791-08-0 (generic)	PEG-5 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 5.	surfactant - emulsifying agent
PEG-6 Cocamide 61791-08-0 (generic)	PEG-6 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 6.	surfactant - emulsifying agent
PEG-7 Cocamide 61791-08-0 (generic)	PEG-7 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 7.	surfactant - emulsifying agent
PEG-11 Cocamide 61791-08-0 (generic)	PEG-11 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 11.	surfactant - cleansing agent; surfactant - emulsifying agent
PEG-20 Cocamide 61791-08-0 (generic)	PEG-20 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 20.	surfactant - emulsifying agent
PEG-3 Cocamide DEA	PEG-3 Cocamide DEA is the polyethylene glycol derivative of Cocamide DEA with an average of 3 moles of ethylene oxide. [Cocamide DEA is a mixture of ethanolamides of coconut acid. It conforms generally to the above formula, and RCO- represents the fatty acids derived from <i>Cocos nucifera</i> (coconut) oil.]	surfactant - emulsifying agent
PEG-20 Cocamide MEA	PEG-20 Cocamide MEA is the polyethylene glycol derivative of cocamide MEA containing an average of 20 moles of ethylene oxide. [Cocamide MEA is a mixture of ethanolamides of coconut acid. It conforms generally to the above general formula, and RCO- represents the fatty acids derived from <i>Cocos nucifera</i> (coconut) oil.]	surfactant - emulsifying agent

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.¹ CIR Staff

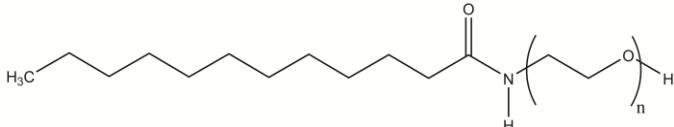
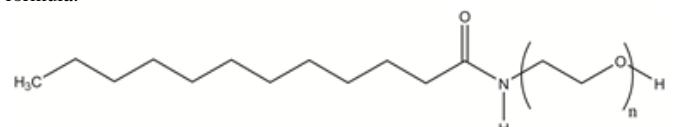
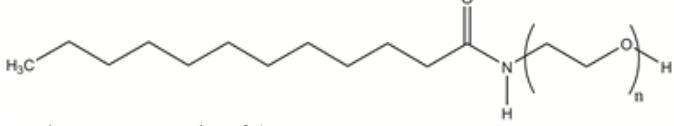
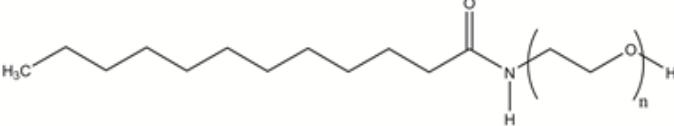
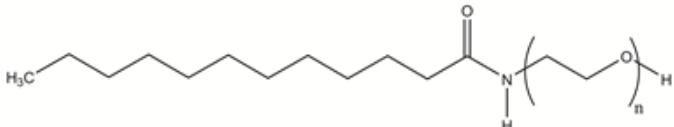
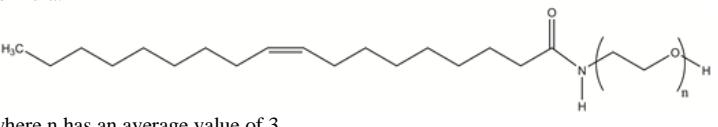
Ingredient CAS No.	Definition & Structure	Function(s)
PEG-6 Hydrogenated Palmamide	PEG-6 Hydrogenated Palmamide is the polyethylene glycol amide of hydrogenated palm oil that generally to the above formula, and RCO- represents the fatty acids derived from hydrogenated palm oil and n has an average value of 6.	emulsion stabilizer; surfactant - emulsifying agent
PEG-50 Hydrogenated Palmamide	PEG-50 Hydrogenated Palmamide is the polyethylene glycol amide of hydrogenated palm oil that conforms generally to the above formula, and RCO- represents the fatty acids from hydrogenated palm oil and n has an average value of 50.	cleansing agent; surfactant - solubilizing agent
PEG-13 Hydrogenated Tallow Amide 68783-22-2 (generic)	PEG-13 Hydrogenated Tallow Amide is the polyethylene glycol amide of hydrogenated tallow amide that conforms generally to the above formula, and RCO- represents the fatty acids derived from hydrogenated tallow and n has an average value of 13.	surfactant - emulsifying agent
PEG-5 Lanolinamide	PEG-5 Lanolinamide is the polyethylene glycol amide of lanolin acid with an average of 5 [stoichiometric equivalents] of ethylene oxide. [PEG-5 Lanolinamide conforms generally to the above formula, and RCO- represents the fatty acids derived from Lanolin Acid (a mixture of organic acids obtained from the hydrolysis of Lanolin) and n has an average value of 5.]	hair conditioning agent; viscosity increasing agent - nonaqueous
PEG-2 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-2 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula: 	surfactant - cleansing agent; surfactant - emulsifying agent
PEG-3 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-3 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula: 	surfactant - emulsifying agent; surfactant - foam booster
PEG-5 Lauramide 26635-75-6 (generic)	PEG-5 Lauramide is the polyethylene glycol amide of lauric acid that conforms generally to the formula: 	surfactant - emulsifying agent
PEG-6 Lauramide 26635-75-6 (generic)	PEG-6 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula: 	surfactant - emulsifying agent
PEG-11 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-11 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula: 	surfactant - emulsifying agent
PEG-3 Oleamide	PEG-3 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula: 	surfactant - emulsifying agent; surfactant - foam booster

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.¹ CIR Staff

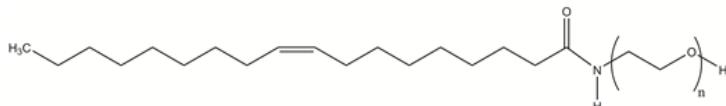
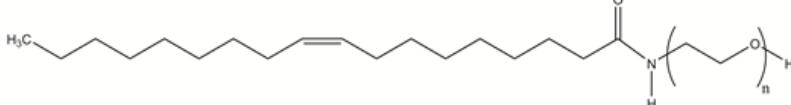
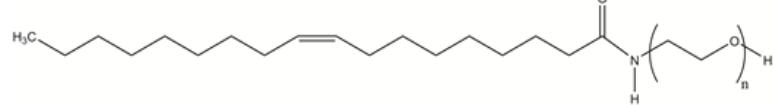
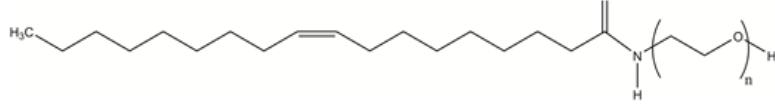
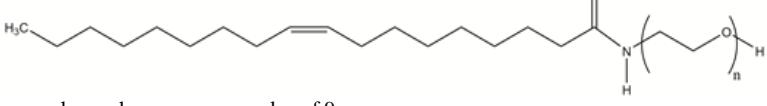
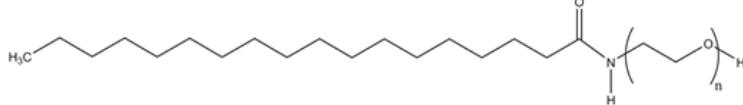
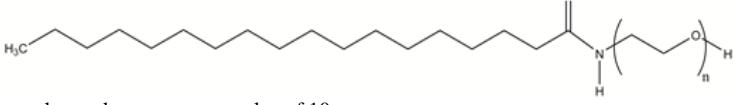
Ingredient CAS No.	Definition & Structure	Function(s)
PEG-4 Oleamide	PEG-4 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 4.	surfactant - emulsifying agent
PEG-5 Oleamide	PEG-5 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 5.	surfactant - emulsifying agent
PEG-6 Oleamide	PEG-6 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 6	surfactant - emulsifying agent
PEG-7 Oleamide	PEG-7 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 7.	surfactant - emulsifying agent
PEG-9 Oleamide	PEG-9 Oleamide is the polyethylene glycol amide of oleic acid that conforms generally to the formula:  where n has an average value of 9.	surfactant - emulsifying agent
PEG-4 Rapeseedamide 85536-23-8	PEG-4 Rapeseedamide is the polyethylene glycol amide of the fatty acids derived from rapeseed oil with an average of 4 moles of ethylene oxide. [Rapeseed Acid is a mixture of fatty acids derived from <i>Brassica campestris</i> (rapeseed) seed oil. PEG-4 Rapeseedamide conforms generally to the above general formula, and RCO- represents the fatty acids from rapeseed oil and n has an average value of 4.]	surfactant - emulsifying agent; viscosity increasing agent - aqueous
PEG-4 Stearamide	PEG-4 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:  where n has an average value of 4.	surfactant - emulsifying agent
PEG-10 Stearamide	PEG-10 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:  where n has an average value of 10.	surfactant - emulsifying agent
PEG-15 Stearamide	PEG-15 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:	surfactant - emulsifying agent

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.¹ CIR Staff

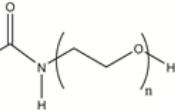
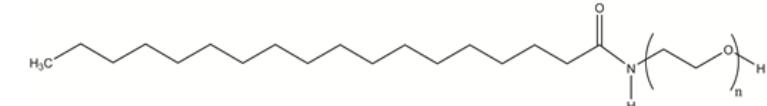
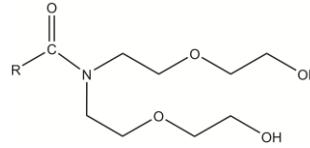
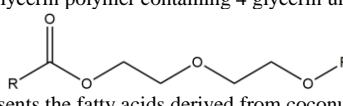
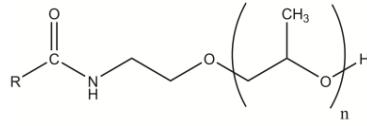
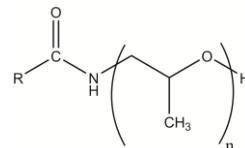
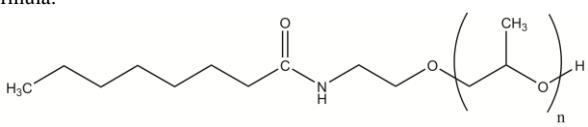
Ingredient CAS No.	Definition & Structure	Function(s)
PEG-50 Stearamide 8051-61-4	 <p>where n has an average value of 15.</p> <p>PEG-50 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:</p>  <p>where n has an average value of 50.</p>	skin-conditioning agent - miscellaneous
PEG-5 Tallow Amide 8051-61-4	<p>PEG-5 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 5.</p>	antistatic agent; surfactant - emulsifying agent
PEG-8 Tallow Amide 8051-63-6	<p>PEG-8 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 8.</p>	surfactant - emulsifying agent
PEG-50 Tallow Amide 8051-63-6	<p>PEG-50 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 50.</p>	surfactant - cleansing agent; surfactant - solubilizing agent
PEG-2 Tallowamide DEA 8051-63-6	<p>PEG-2 Tallowamide DEA is the polyethylene glycol amine derived from tallow acid that conforms generally to the formula:</p>  <p>where RCO- represents tallowoyl moiety.</p>	surfactant - cleansing agent
Ethoxylated Polyglyceryl		
Polyglyceryl-4-PEG-2 Cocamide 201363-52-2	<p>Polyglyceryl-4-PEG-2 Cocamide is an ether of PEG-2 cocamide and polyglycerin-4. [Polyglycerin-4 is a glycerin polymer containing 4 glycerin units.]</p>  <p>[wherein RCO- represents the fatty acids derived from coconut oil and R' represents polyglyceryl-4.]</p>	surfactant - emulsifying agent
Propoxylated		
PPG-2 Hydroxyethyl Cocamide 201363-52-2	<p>PPG-2 Hydroxyethyl Cocamide is the organic compound that conforms generally to the formula:</p>  <p>where RCO- represents the fatty acids derived from coconut oil and n has an average value of 2.</p>	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous
PPG-2 Cocamide 201363-52-2	<p>PPG-2 Cocamide is the dipropylene glycol amide of coconut acid that conforms generally to the formula:</p>  <p>where n has an average value of 2 and RCO- represents the cocoyl moiety.</p>	surfactant - foam booster; viscosity increasing agent - aqueous
PPG-1 Hydroxyethyl Caprylamide 201363-52-2	<p>PPG-1 Hydroxyethyl Caprylamide is the organic compound that conforms generally to the formula:</p>  <p>where n has an average value of 1.</p>	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.¹ CIR Staff

Ingredient CAS No.	Definition & Structure	Function(s)
PPG-2 Hydroxyethyl Coco/Isostearamide	PPG-2 Hydroxyethyl Coco/Isostearamide is the organic compound that conforms generally to the formula: 	surfactant - cleansing agent; surfactant - foam booster; surfactant - solubilizing agent; viscosity increasing agent - aqueous
PPG-3 Hydroxyethyl Soyamide	PPG-3 Hydroxyethyl Soyamide is the organic compound that conforms to the formula: 	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous

Table 3 Physical and Chemical Properties

Property	Value	Reference
PEG-6 Cocamide		
Physical Form (@ 25°C)	liquid	17
Color (@ 30°C)	clear	18
Density (g/ml @ 25 °C)	0.99	17,18
Viscosity (kg/(s x m) @ 25°C; @ 60°C)	0.217; 0.039	18
Vapor pressure (mmHg @ 20 °C)	0.01	17
Boiling Point (°C)	100	17
HLB	14.6	17,18
PEG-4 Rapeseedamide (60-80% purity)		
Physical Form	clear liquid	6
Color	yellow	6
Molecular Weight (g/mol)	< 600	3
Density/Specific Gravity (kg/m ³ ; @ 20°C)	997	3
Vapor pressure (mm Hg @ °C)	0.0019	3
Melting Point (°C)	5-10	3
Boiling Point (°C)	> 262	3
Water Solubility (g/L @ 23 °C)	9.0 x 10 ⁻⁴	3
Other Solubility (g/L @ 20°C)	652 – 702 in n-octanol	3
log K _{ow}	2.6	3
HLB	~11	6
PPG-2 Hydroxyethyl Cocamide		
Physical Form	liquid	4
Color	yellowish	4
Specific Gravity (@ 20 °C)	0.98	4
Vapor pressure (mmHg 25 °C)	5.25 x 10 ⁻⁵	4
Boiling Point (°C)	> 165 (decomposition occurs over the range 60-305)	4
Water Solubility (g/L @ 20 °C)	< 0.001	4
log K _{ow}	0.86 to > 6.2 (likely due to the variability of cocamide chain lengths)	4

Table 4. Frequency and concentration of use according to duration and type of exposure

	# of Uses ⁸ PEG-2 Cocamide	Max Conc of Use (%) ⁹	# of Uses ⁸ PEG-3 Cocamide	Max Conc of Use (%) ⁹	# of Uses ⁸ PEG-5 Cocamide	Max Conc of Use (%) ⁹
Totals*	2	0.12-2	2	NR	21	NR
Duration of Use						
Leave-On	NR	NR	1	NR	NR	NR
Rinse-Off	2	0.12-2	1	NR	24	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	1 ^a	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	2	0.3-2	1	NR	19	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.13	NR	NR	2	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.3-2	NR	NR	19	NR
Baby Products	NR	NR	NR	NR	NR	NR
	PEG-6 Cocamide		PEG-50 Hydrogenated Palmamide		PEG-6 Lauramide	
Totals*	19	0.75-2	26	1-3	NR	4
Duration of Use						
Leave-On	3	NR	NR	1	NR	NR
Rinse Off	16	0.75-2	26	2-3	NR	4
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	1 ^a ; 1 ^b	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	1 ^b	NR	NR	NR	NR	NR
Dermal Contact	11	2	NR	NR	NR	4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	4	0.75-0.8	NR	1	NR	NR
Hair-Coloring	4	NR	26	2-3	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	8	NR	NR	NR	NR	4
Baby Products	NR	NR	NR	NR	NR	NR
	PEG-4 Rapeseedamide		PEG-50 Tallow Amide		PPG-2 Cocamide	
Totals*	280	0.93-9.3	NR	2	3	0.8-4
Duration of Use						
Leave-On	3	NR	NR	NR	NR	0.8
Rinse-Off	274	0.93-9.3	NR	2	3	2-4
Diluted for (Bath) Use	3	2	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	1	NR	NR	NR	NR	0.8
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	52	0.93-3	NR	NR	1	4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	51	2.4-2.8	NR	NR	2	0.8-2
Hair-Coloring	174	8.2-9.3	NR	2	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	54	1-3	NR	NR	NR	4
Baby Products	NR	NR	NR	NR	NR	NR

Table 4. Frequency and concentration of use according to duration and type of exposure

	# of Uses ⁸	Max Conc of Use (%) ⁹	# of Uses ⁸	Max Conc of Use (%) ⁹	# of Uses ⁸	Max Conc of Use (%) ⁹
	PPG-2 Hydroxyethyl Cocamide		PPG-2 Hydroxyethyl Coco/Isostearamide			
Totals	342	0.00025-7.5	23	0.5-0.6		
Duration of Use						
Leave-On	10	0.35-7.5	NR	NR		
Rinse Off	326	0.00025-4	23	0.5-0.6		
Diluted for (Bath) Use	6	1.5-3	NR	NR		
Exposure Type						
Eye Area	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation-Spray	1 ^a	0.62 ^a	NR	NR		
Incidental Inhalation-Powder	NR	0.35-3 ^c	NR	NR		
Dermal Contact	309	0.008-4	12	0.5-0.6		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	33	0.00025-7.5	11	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	286	1.5-3	6	0.5-0.6		
Baby Products	2	NR	NR	NR		

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

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

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

^c It is possible these products are powders, but it is not specified whether the reported uses are powders

NR – no reported use

Table 5. Ingredients not reported to be in use (according to VCRP and Council survey data)

PEG-4 Cocamide	PEG-3 Lauramide	PEG-4 Stearamide
PEG-7 Cocamide	PEG-5 Lauramide	PEG-10 Stearamide
PEG-11 Cocamide	PEG-11 Lauramide	PEG-15 Stearamide
PEG-20 Cocamide	PEG-3 Oleamide	PEG-50 Stearamide
PEG-3 Cocamide DEA	PEG-4 Oleamide	PEG-5 Tallow Amide
PEG-20 Cocamide MEA	PEG-5 Oleamide	PEG-8 Tallow Amide
PEG-6 Hydrogenated Palmamide	PEG-6 Oleamide	PEG-2 Tallowamide DEA
PEG-13 Hydrogenated Tallow Amide	PEG-7 Oleamide	Polyglyceryl-4-PEG-2 Cocamide
PEG-5 Lanolinamide	PEG-9 Oleamide	PPG-1 Hydroxyethyl Caprylamide
PEG-2 Lauramide	PEG-5 Oleamide Dioleate	PPG-3 Hydroxyethyl Soyamide

Table 6. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose	Protocol	LD ₅₀ or LC ₅₀ /Results	Reference
DERMAL							
PEG-4 Rapeseedamide (60 - 80% pure)	Sprague-Dawley rats	5/sex	none specified	2000 mg/kg	semi-occlusive application (OECD TG 402)	> 2000 mg/kg no dermal irritation and no signs of toxicity were observed	³
PPG-2 Hydroxyethyl Cocamide	Sprague-Dawley rats	5/sex	none specified	2000 mg/kg	50 cm ² porous gauze pad with waterproof dressing, (OECD TG 402)	> 2000 mg/kg slight to well-defined erythema (7 animals) and edema (6 animals) was resolved by day 9 and 8, respectively; desquamation with scabbing was observed in 2 females	⁴
ORAL							
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	5/sex	none specified	2000 mg/kg	by gavage (OECD TG 401)	> 2000 mg/kg no signs of toxicity were observed	³
PPG-2 Hydroxyethyl Cocamide	Sprague-Dawley rats	3/sex	none specified	2000 mg/kg	by gavage (OECD TG 401)	> 2000 mg/kg	⁴
PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across)	Sprague-Dawley rats	3/sex	1% (w/v) aq. methylcellulose	2000 mg/kg	by gavage (OECD TG 423)	> 2000 mg/kg	³
INHALATION							
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	2 males	none specified	24.34 mg/l (nominal); 4.92 mg/l (actual)	oronasal exposure (OECD TG 403) 0.5, 1, 2, or 4 h exposure period 2.14 µm particle size	1-5 mg/L/4 h labored and noisy breathing was observed 1 animal exposed for 2 h and 1 exposed for 4 h died 1 day after exposure; discolored non-collapsed lungs, mottled liver, dilatation of the kidneys and intestine were observed at necropsy	³
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	3/sex	none specified	119 mg/l (nominal); 6 mg/l (actual)	oronasal exposure (OECD TG 436) 4 h exposure period; 2.05-2.14 µm particle size	6 mg/L/4 h labored breathing was observed in all males and in one female (day 2); no mortality	³

Abbreviations: OECD – Organisation for Economic Co-operation and Development; TG – test guideline

Table 7. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
PEG-4 Rapeseedamide (60 - 80% pure)	312.5 - 5000 µg/plate, with and without metabolic activation	DMSO	<i>Salmonella typhimurium</i> TA1538, TA1535, TA1537, TA98, TA100	Ames test (OECD TG 471)	not mutagenic	³
PEG-4 Rapeseedamide (60 - 80% pure)	39 - 5000 µg/ml, with and without metabolic activation	DMSO	human cultured peripheral lymphocytes	mammalian chromosomal aberration test (OECD TG 473)	not clastogenic	³
PPG-2 Hydroxyethyl Cocamide	1.5 - 5000 µg/plate, with and without metabolic activation	not stated	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 <i>Escherichia coli</i> CM891	Ames test (OECD TG 471)	not mutagenic	⁴
PPG-2 Hydroxyethyl Cocamide	<u>with activation:</u> 125 - 300 µg/ml initial study; 3 h); 300 - 500 µg/ml (confirmation; 3 h); 450 and 500 µg/ml (confirmation 2; 3 h) <u>without metabolic activation:</u> 62.5 - 250 µg/ml (initial study; 3 h); 62.5 - 125 µg/ml (confirmation; 21 h)	water	human lymphocytes	mammalian chromosomal aberration test (OECD TG 473)	"not likely to be clastogenic" with metabolic activation, statistically significant increase in proportion of metaphase figures with chromosomal aberrations at 450 and 500 µg/ml in both confirmation studies; these were cytotoxic concentrations all other results were negative	⁴
PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across)	5 - 5000 µg/plate, with and without metabolic activation	DMSO	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 <i>Escherichia coli</i> WP2uvrA	Ames test (OECD TG 471)	not mutagenic	⁵
IN VIVO						
PEG-4 Rapeseedamide (60-80% pure)	0, 100, 200, and 400 mg/kg bw (24 h) 0 and 400 mg/kg bw (48 h)	arachis oil	albino Crl:CD-1 mice; 7/sex test animals; 14/sex negative controls; 5/sex positive controls	micronucleus test (OECD TG 474) animals were dosed by gavage cyclophosphamide served as the positive control	not clastogenic no statistically significant decreases in PCE/NCE ratios; however, marked decreases in the PCE/NCE ratio was observed in the 200 (24h) and 400 (48 h) mg/kg bw groups clinical signs were reported in the 200 and 400 mg/kg bw dose groups	³
PPG-2 Hydroxyethyl Cocamide	0, 250, 500, and 1000 mg/kg	water	CD-1 outbred albino mice; 10 males in the control and high dose groups; 5 males in the low and mid dose groups	micronucleus test (OECD TG 474) animals were dosed intraperitoneally positive control not identified	not clastogenic	⁷
PPG-2 Hydroxyethyl Cocamide	0, 600, and 2000 mg/kg	water	Sprague-Dawley rats; 5 males per group	rat liver DNA repair (UDS) test (OECD TG 486) animals were dosed by gavage	did not induce DNA damage	⁴

Abbreviations: DMSO – dimethyl sulfoxide; NCE – normochromatic erythrocytes; OECD – Organisation for Economic Co-operation and Development; PCE – polychromatic erythrocytes; TG – test guideline; UDS – unscheduled DNA synthesis

Table 8. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL					
PEG-4 Rapeseedamide (60 - 80% pure)	applied neat	3 female NZW rabbits	semi-occlusive application; animals were observed for 22 days (OECD TG 404) duration of dosing was not stated; however, according to the TG, dosing is typically 4 h in duration	irritating; no corrosive effect; no systemic toxicity mean scores (calculated using the 24, 48, and 72 h scores for each animal) ranged from 2-4/4 for erythema and 2-2.7/3 for edema irritation did not resolve by study termination	³
PEG-4 Rapeseedamide (60 - 80% pure)	intradermal induction – 0.2% topical induction – 10% topical challenge – 0.01% vehicle – sesame oil	10 (test) or 5 (control) male Dunkin Hartley guinea pigs	skin sensitization – maximization test (OECD TG 406)	not sensitizing	³
HUMAN					
PPG-2 Hydroxyethyl Cocamide	applied neat	3 male NZW rabbits	4 h patch; 0.5 ml applied to a 2.5 cm ² area using a porous gauze pad covered with elastic adhesive dressing (OECD TG 404) 1 animal also received 3 min and 1 h applications	4 h exposure: thickening of the skin, desquamation, and well-defined erythema in all 3 animals; did not resolve in 2/3 animals by day 14 3 min and 1 h exposure: no irritation	⁴
PPG-2 Hydroxyethyl Cocamide	intradermal induction – 0.5% topical induction – 50% topical challenge – 5 and 10% vehicle – water	10 (test) or 5 (control) female Dunkin Hartley guinea pigs	(Magnusson-Kligman maximization test (OECD TG 406) intradermal induction (day 0) consisted of 3 pairs of injections: FCA/water 1:1; test substance only; test substance in FCA/saline 1:1 topical induction (day 7), 48 h occlusive patch (0.4 ml) challenge (day 21), 24 h occlusive patches (0.2 ml)	not sensitizing no irritation following topical applications; slight irritation at injection site after injection of test substance or sterile water (control animals)	⁴
PEG-4 Rapeseedamide (60 - 80% pure)	0.5% aq.	50 subjects	HRIFT induction: 2 cm ² patches containing 0.2 ml test material were applied for 24 h (3x/wk for 3 wks), and the test sites were assessed 24 or 48 h after removal challenge: after a 2 wk non-treatment period, 1 test patch was applied for 24 h to a previously untreated site; the site was assessed 24, 48, and 72 h after application	not an irritant or sensitizer one instance of barely perceptible or spotty erythema for 3 subjects o	³
PPG-2 Hydroxyethyl Cocamide	5% aq.	50 subjects	48 h occlusive patch; 0.2 applied via a 4.5 cm ² gauze pad; test sites were evaluated at patch removal and after 24 h procedure was repeated using occlusive and semi-occlusive patches in subjects with positive responses	not irritating one subject had a mild and one a moderate response 24 h after patch removal; both subjects had mild responses 48 h after patch removal with follow-up testing, one subject had a positive response with the occlusive patch, but a negative response with the semi-occlusive patch	⁴

Abbreviations: aq. – aqueous; NZW – New Zealand White; HRIFT – human repeated insult patch test; OECD – Organisation for Economic Co-operation and Development; TG – test guideline

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