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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 40 alkoxylated fatty amides as used in cosmetics. These ingredients are structurally related as alkoxylated simple amides, and all but a few of these ingredients are reported to function in cosmetics as surfactants – emulsifying agents. The Panel reviewed the relevant data for these ingredients, and concluded that these alkoxylated fatty amides are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

INTRODUCTION

This assessment reviews the safety of 40 alkoxylated fatty amides, listed below, as used in cosmetics. 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 1).[1]

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

The rationale for this grouping of ingredients stems from the fact that these ingredients are structurally related as *N*-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 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-irritating[2]), most of these alkoxylated fatty amides are mono-*N*-alkoxyl-substituted. These ingredients have classic surfactant structures, with a hydrophobic, fatty alkyl tail on one end and a hydrophilic, non-ionic alkoxylated head group on the other end.

The Panel has reviewed the safety of some of the components of these ingredients. In 2010, CIR issued a final report on the safety of polyethylene glycols (PEGs); the Panel concluded that the PEGs are safe in the present practices of use and concentration.[3] In 2012, CIR published a report on the safety of polypropylene glycols (PPGs), with a conclusion that PPGs are safe in the present practices of use and concentration when formulated to be non-irritating.[4] Additionally, the safety of diethanolamides has been reviewed by CIR. In 2013, diethanolamides, including Cocamide DEA and Tallowamide DEA, were found to be safe in the present practices of use and concentration when formulated to be non-irritating, and when the levels of free DEA in the diethanolamides do not to exceed the present practices of use and concentration of DEA itself.[5] Finally, in 2015, the Panel issued a safety assessment on the (mono-) ethanolamides, including Cocamide MEA, with the conclusion that the ethanolamides are safe in the present practices of use and concentration when formulated to be non-irritating.[6] Both the ethanolamides and the diethanolamides should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

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.

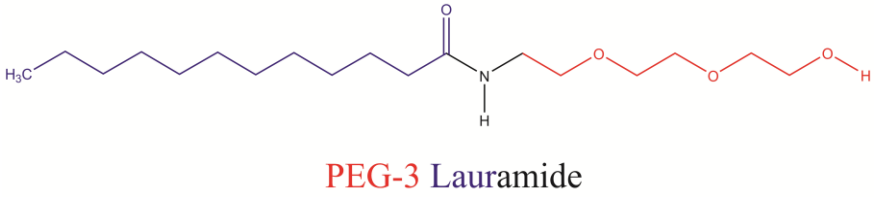
Much of the data included in this safety assessment were obtained from Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) hazard assessments.[7-9] These data summaries are available on the NICNAS website, and when deemed appropriate, information from the summaries has 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 1. Provided in Table 2 are the total fatty acid compositions of relevant plant-derived fatty acid oils,[10-12] and of lanolin[13] and tallow.[14]

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 mono-substituted ingredients reviewed in this report are classic non-ionic surfactants, with a hydrophobic fatty alkyl tail on one end and a hydrophilic non-ionic alkoxylated head group on the other end (Figure 1). The di-substituted ingredients herein, however, comprise two alkoxylations at the head group (Figure 2).



PEG-3 Lauramide

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

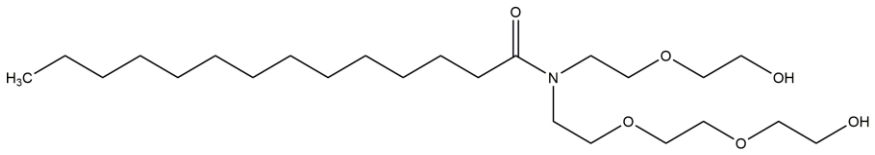


Figure 2. Example of a fatty acid amide (lauramide), and its di-alkoxylated (PEG-3 DEA) surfactant structure (PEG-3 Cocamide DEA is a mixture of fatty acid amides, but the highest concentration constituent therein is the lauramide).

Physical and Chemical Properties

PEG-6 Cocamide,[15,16] PEG-4 Rapeseedamide,[17] and PPG-2 Hydroxyethyl Cocamide[7] present as clear liquids that are generally yellow in color. Physical and chemical properties of these ingredients are listed in Table 3.

Method of Manufacture

PEG-50 Hydrogenated Palmamide

According to one supplier, PEG-50 Hydrogenated Palmamide is manufactured by ethoxylating a monoethanol amide with approximately 50 stoichiometric equivalents of ethylene oxide.[18] Vegetable and synthetic raw materials are used.

PPG-2 Cocamide

PPG-2 Cocamide is reported to be manufactured by a propoxylated reaction of cocoyl monoisopropanol amide with approximately 1 stoichiometric equivalent of propylene oxide.[19] PPG-2 Cocamide is based on plant and synthetic raw materials.

PPG-2 Hydroxyethyl Coco/Isostearamide

PPG-2 Hydroxyethyl Coco/Isostearamide is produced as a result of combining two intermediates from two separate reactions; one reaction starts with coconut oil + MEA, and the other starts with isostearic acid + MEA.[20] The total process scheme is as follows:

coconut oil + MEA → cocamide → cocamide + propylene oxide → intermediate 1

isostearic acid + MEA → isostearyl amide MEA → isostearyl amide MEA + propylene oxide → intermediate 2

intermediate 1 + intermediate 2 → PPG-2 Hydroxyethyl Coco/Isostearamide

Impurities

PEG-50 Hydrogenated Palmamide

Gas chromatography/mass spectrometry (GC/MS) was used to determine the potential levels of residual monoethylene glycol and diethylene glycol in PEG-50 Hydrogenated Palmamide.[18] Upon analysis, it was reported that PEG-50 Hydrogenated Palmamide contained less than 50 ppm of either substance.

PEG-4 Rapeseedamide

A supplier reports that PEG-4 Rapeseedamide is 92 - 93% "active matter;"[17] specifications for the presence of 1,4-dioxane are 1 ppm maximum.[21] According to another source, the "degree of purity" of PEG-4 Rapeseedamide (as the raw material) is reported to be 60 - 80%.[8] 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."

PPG-2 Hydroxyethyl Cocamide

According to an unpublished data submission, PPG-2 Hydroxyethyl Cocamide is reported to be > 90% pure.[22] Methanol levels are typically < 300 ppm, and heavy metals testing reported levels of < 0.5 ppm.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this safety assessment is evaluated based on data received from the US 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 2018,[23] and data received in response to a Council survey of the maximum reported use concentration by category conducted in 2015,[24] indicate that 11 of the 40 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).[23] 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.[24] 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 0.35% PPG-2 Hydroxyethyl Cocamide in face and neck products.[24]

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 both the 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%.[24] 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.[25,26] 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.[27,28]

The alkoxylated fatty amides are not restricted from use in any way under the rules governing cosmetic products in the European Union.[29]

Non-Cosmetic

PEG-4 Rapeseedamide is used in industrial dishwashing and laundry care.[30]

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 below[7-9,31] are described in Table 6**Error! Reference source not found.**.

The dermal LD_{50}s of PEG-4 Rapeseedamide (60 - 80% pure) and PPG-2 Hydroxyethyl Cocamide in Sprague-Dawley rats were > 2000 mg/kg. In rats, the oral LD_{50}s 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 oral 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 study, but not the second study, and the LC_{50}s 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.[8] All animals survived until study termination. A statistically significant reduction 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.[7] 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.[7] 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.

Exposure Assessment

PEG-4 Rapeseedamide

NICNAS calculated a margin of exposure (MOE) for the use of PEG-4 Rapeseedamide in cosmetic products.[8] Considering simultaneous daily use of six rinse-off product types containing 8% PEG-4 Rapeseedamide (i.e., makeup remover, shower gel, hand washing soap, shampoo, conditioner, and facial cleanser), assuming 100% dermal absorption, and assuming an adult body weight of 60 kg, NICNAS estimated a daily systemic exposure of 1.38 mg/kg bw/day. NICNAS also calculated

an equivalent daily systemic exposure of 0.10 mg/kg bw/day for a hair dye containing 15% PEG-4 Rapeseedamide. Combining these two exposures, the total potential systemic exposure was 1.48 mg/kg bw/day. (It should be noted that the concentrations used to calculate daily exposure by NICNAS are greater than those reported in the Council use survey.) For the MOE calculation, NICNAS used the NOAEL that was calculated for female rats (i.e., 150 mg/kg bw/day PEG-4 Rapeseedamide), because the effects at 15 mg/kg bw/day (which was the NOAEL for male rats) were minimal.

MOE = NOAEL / exposure
= 150 mg/kg bw/day / 1.48 mg/kg bw/day
= 101

According to the NICNAS assessment, a MOE value ≥ 100 is considered acceptable to account for intra- and inter-species differences. Therefore the MOE for PEG-4 Rapeseedamide was considered acceptable.

PPG-2 Hydroxyethyl Cocamide

NICNAS evaluated exposure to PPG-2 Hydroxyethyl Cocamide through shampoo use.[7] Assuming application of 12 g of shampoo containing 4% PPG-2 Hydroxyethyl Cocamide, a body weight of 60 kg, and 10% dermal absorption, exposure is calculated as 0.8 mg/kg/d PPG-2 Hydroxyethyl Cocamide. The NOEL in a 28-day oral study in rats of PPG-2 Hydroxyethyl Cocamide was determined to be 15 mg/kg/d; the calculated human exposure is below the NOEL value.

The CIR Science and Support Committee (SSC) calculated MOEs for a leave-on face product containing 0.35% and for a leave-on hair styling product containing 7.5% PPG-2 Hydroxyethyl Cocamide.[32] Assuming the 95th percentile use of a face lotion (3.99 g/day), the estimated exposure from a face product containing 0.35% PPG-2 Hydroxyethyl Cocamide is 0.24 mg/kg bw/d. For the hair product containing 7.5% PPG-2 Hydroxyethyl Cocamide (5.74 mg/kg bw/d), the estimated exposure is 0.43 mg/kg bw/d. For the MOE calculations, the CIR SSC used the most conservative NOAEL value from a 28-day oral toxicity study that was available for this group of ingredients, which was 150 mg/kg bw/day from the study on PEG-4 Rapeseedamide. (In the 28-day oral rat study of PPG-2 Hydroxyethyl Cocamide, the NOAEL was 1000 mg/kg/day.)

MOE for the face product = 150 mg/kg/bw / 0.24 mg/kg bw/day
= 625

MOE for leave-on hair product = 150 mg/kg/bw / 0.43 mg/kg bw/day
= 349

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, 150, or 500 mg/kg bw/day PEG-4 Rapeseedamide (60 - 80% pure) in arachis oil by gavage for 55 days.[8] 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 below[7-9] 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 ≤ 400 mg/kg bw in arachis oil[8] and aq. PPG-2 Hydroxyethyl Cocamide dosed intraperitoneally at ≤ 1000 mg/kg were not clastogenic.[7] 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[7,8,33,34] 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. Undiluted PPG-2 Hydroxyethyl Cocamide applied to rabbit skin for 4 h (2.5 cm^2 patches containing 0.5 ml test material) was classified as irritating, produced thickening of the skin, desquamation, and well-defined erythema, but 3-min and 1-h exposures 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; 2 cm^2 patches containing 0.2 ml test material) was not a sensitizer in a human repeated insult patch test (HRIPT), and 5% aq. PPG-2 Hydroxyethyl Cocamide (4.5 cm^2 patches containing 0.2 ml test material) 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).[8] 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 (all animals)/1 for discharge; irritation resolved within 7 days. Corneal opacity and iridial 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.[7] 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.[35] 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 40 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 non-ionic surfactants, with a hydrophobic fatty alkyl tail on one end and a hydrophilic, non-ionic, alkoxylated head group on the other end.

According to one supplier, PEG-50 Hydrogenated Palmamide is manufactured by ethoxylating a monoethanol amide with ethylene oxide. PPG-2 Cocamide is reported to be manufactured by a propoxylated reaction of cocoyl monoisopropanol amide with propylene oxide. PPG-2 Hydroxyethyl Coco/Isostearamide is produced as a result of combining two intermediates from two separate reactions; one reaction starts with coconut oil + MEA, and the other starts with isostearic acid + MEA.

Using GC/MS analysis, PEG-50 Hydrogenated Palmamide contains less than 50 ppm of residual monoethylene glycol or diethylene glycol. One supplier reports that PEG-4 Rapeseedamide is 92 - 93% active matter, and specifications for the presence of 1,4-dioxane are 1 ppm. According to another source, the degree of purity of PEG-4 Rapeseedamide (as the raw

material) is 60 – 80% pure and low levels of 1,4 dioxane (down to 100 mg/kg or 100 mg/l) may be present. PPG-2 Hydroxyethyl Cocamide is reported to be > 90% pure; methanol levels are typically < 300 ppm, and heavy metals testing reported levels of < 0.5 ppm

Eleven of the 40 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 0.35% PPG-2 Hydroxyethyl Cocamide in face and neck 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 LD_{50}s of PEG-4 Rapeseedamide (60 - 80% pure) and PPG-2 Hydroxyethyl Cocamide in Sprague-Dawley rats were > 2000 mg/kg. In rats, the oral LD_{50}s 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 oral 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 LC_{50}s 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.

MOE were calculated for PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide. The MOE for PEG-4 Rapeseedamide, considering combined use in six rinse-off products and in a hair dye, was 101; a MOE value ≥ 100 is considered acceptable to account for intra- and inter-species differences. For PPG-2 Hydroxyethyl Cocamide, an MOE of 625 was calculated for a face product containing 0.35%, and a MOE of 349 was calculated for a leave-on hair styling product containing 7.5% PPG-2 Hydroxyethyl Cocamide.

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. Undiluted PPG-2 Hydroxyethyl Cocamide applied to rabbit skin for 4 h (2.5 cm^2 patches containing 0.5 ml test material) was classified as irritating, produced thickening of the skin, desquamation, and well-defined erythema, but 3-min and 1-h exposures 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; 2 cm^2 patches containing 0.2 ml test material) was not a sensitizer in an HRIPT, and 5% aq. PPG-2 Hydroxyethyl Cocamide (4.5 cm^2 patches containing 0.2 ml test material) 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.

DISCUSSION

This report reviews the safety of 40 cosmetic ingredients that are structurally related as alkoxylated simple amides. Dermal absorption and dermal toxicity data are lacking in this report; however, the Panel stated that the oral 28-day toxicity studies on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide, and the developmental and reproductive toxicity data on PEG-4 Rapeseedamide, provide sufficient information on the systemic toxicity potential of these ingredients. Oral administration is expected to result in higher concentrations in the blood than would occur with dermal absorption of these ingredients, and the dermal use concentrations are relatively low. Additionally, the MOE for PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide were acceptable. Therefore, concerns regarding dermal toxicity were mitigated.

The Panel determined that the information on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide (which are the two ingredients with the highest reported frequency of use) could be read-across to the entire group. Also, the Panel determined that the information on the mono-*N*-alkoxyl-substituted ingredients informs the safety of the di-*N*,*N*-alkoxyl-substituted ingredients that are included in this report.

The Panel remarked on the lack of carcinogenicity data. Concerns for this lack of data, however, were mitigated by the sufficient, negative genotoxicity studies and lack of structural alerts for carcinogenicity.

The Panel noted that CIR has issued reports on the component parts of these polyalkoxylated ethanolamides. Specifically, the polyalkoxyl moieties PEGs and PPGs have been found safe and safe when formulated to be non-irritating in the present practices of use and concentration, respectively. Mono- and diethanolamides (e.g, Cocamide MEA and Cocamide DEA) are safe in the present practices of use and concentration when formulated to be non-irritating, and these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed. For the diethanolamides, the levels of free DEA are not to exceed the present practices of use and concentration of DEA itself.

The Panel also discussed the issues of impurities that could be of concern with this group of ingredients. The possible presence of 1,4-dioxane as an impurity is one concern. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit this impurity in alkoxylated fatty amide ingredients before blending them into cosmetic formulations. Additionally, manufacturers should minimize primary amine impurities, and the Panel specified that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed. The Panel acknowledged that some of the alkoxylated fatty amides may be formed from plant-derived or animal-derived constituents. The Panel thus expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to sufficiently limit amounts of such impurities in these ingredient before blending them into cosmetic formulations. Additionally, the Panel considered the risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. While tallow may be used in the manufacture of some ingredients in this safety assessment and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the US FDA that tallow derivatives are not risk materials for transmission of infectious agents.

PPG-2 Cocamide is used in aerosol hair spray formulations at a maximum concentration of 0.8%, and could possibly be inhaled. Therefore, the Panel discussed the issue of potential inhalation toxicity. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredient is 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 https://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the following 40 alkoxylated fatty amides are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

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

**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.*

TABLES

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

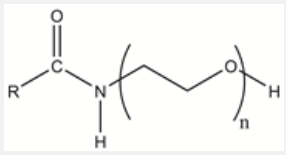
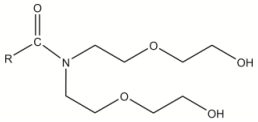
Ingredient CAS No.	Definition & Structure*	Function(s)
Ethoxylated	***General formula:*** 	
PEG-2 Cocamide [61791-08-0 (generic to PEG-x Cocamides)]	PEG-2 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived 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 formula:  where RCO- represents the fatty acids derived from *Cocos nucifera* (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 *Cocos nucifera* (coconut) oil.]	surfactant - emulsifying agent
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

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

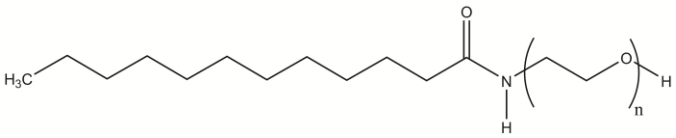
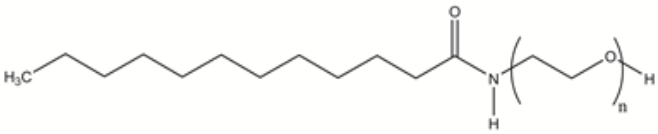
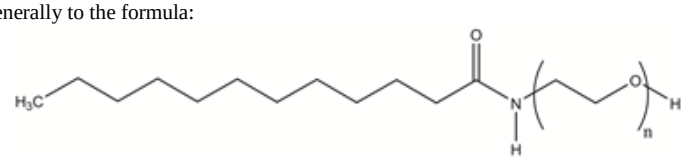
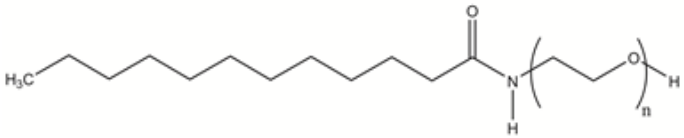
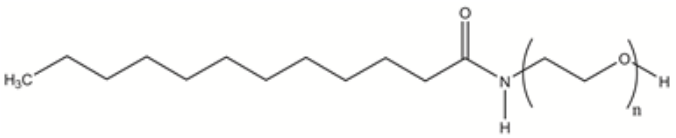
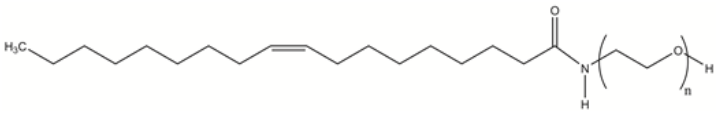
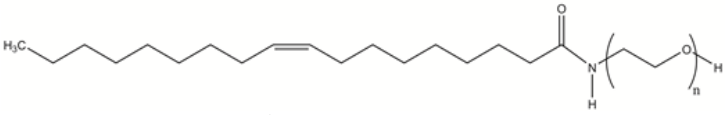
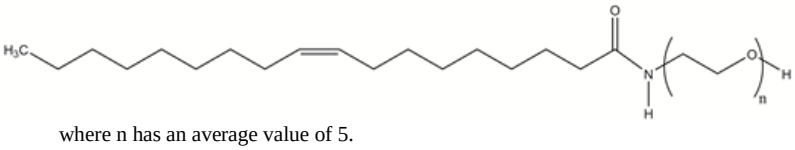
Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-2 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-2 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:  where n has an average value of 2.	surfactant - cleansing agent; surfactant - emulsifying agent
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:  where n has an average value of 3.	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:  where n has an average value of 5.	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:  where n has an average value of 6.	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:  where n has an average value of 11.	surfactant - emulsifying agent
PEG-3 Oleamide	PEG-3 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster
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

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

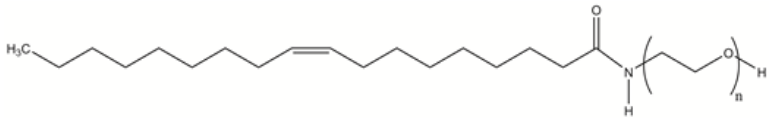
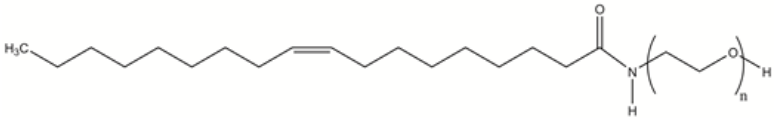
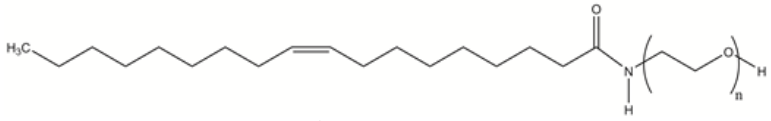
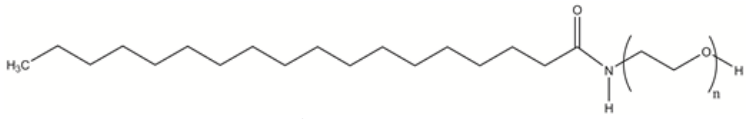
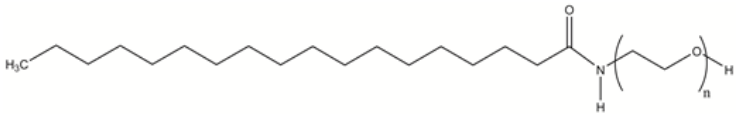
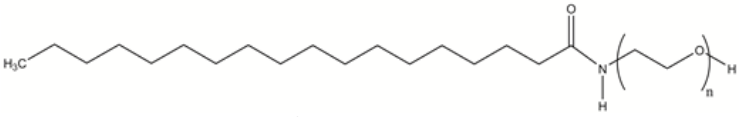
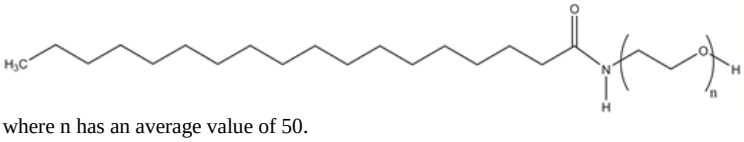
Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-6 Oleamide	PEG-6 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 6	surfactant - emulsifying agent
PEG-7 Oleamide	PEG-7 Oleamide is the polyethylene glycol amide of oleic acid 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 *Brassica campestris* (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:  where n has an average value of 15.	surfactant - emulsifying agent
PEG-50 Stearamide	PEG-50 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:  where n has an average value of 50.	skin-conditioning agent - miscellaneous
PEG-5 Tallow Amide 8051-61-4	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.	antistatic agent; surfactant - emulsifying agent
PEG-8 Tallow Amide	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.	surfactant - emulsifying agent

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

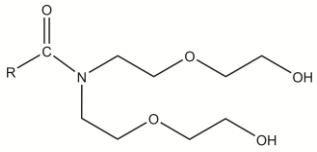
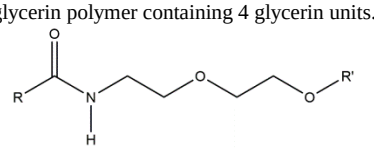
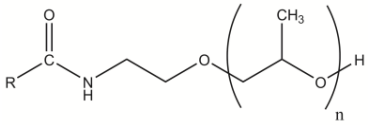
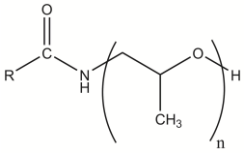
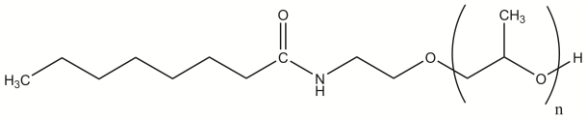
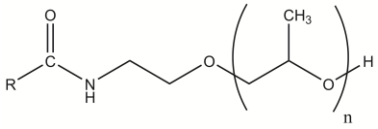
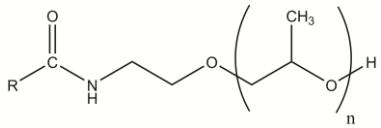
Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-50 Tallow Amide 8051-63-6	PEG-50 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 50.	surfactant - cleansing agent; surfactant - solubilizing agent
PEG-2 Tallowamide DEA	PEG-2 Tallowamide DEA is the polyethylene glycol amine derived from tallow acid that conforms generally to the formula:  where RCO- represents tallowoyl moiety.	surfactant - cleansing agent
Ethoxylated Polyglyceryl		
Polyglyceryl-4-PEG-2 Cocamide	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.]  [wherein RCO- represents the fatty acids derived from coconut oil and R' represents polyglyceryl-4.]	surfactant - emulsifying agent
Propoxylated		
PPG-2 Hydroxyethyl Cocamide 201363-52-2	PPG-2 Hydroxyethyl Cocamide is the organic compound that conforms generally to the formula:  where RCO- represents the fatty acids derived from coconut oil and n has an average value of 2.	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous
PPG-2 Cocamide	PPG-2 Cocamide is the dipropylene glycol amide of coconut acid that conforms generally to the formula:  where n has an average value of 2 and RCO- represents the cocoyl moiety.	surfactant - foam booster; viscosity increasing agent - aqueous
PPG-1 Hydroxyethyl Caprylamide	PPG-1 Hydroxyethyl Caprylamide is the organic compound that conforms generally to the formula:  where n has an average value of 1.	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous
PPG-2 Hydroxyethyl Coco/Isostearamide	PPG-2 Hydroxyethyl Coco/Isostearamide is the organic compound that conforms generally to the formula:  where RCO- represents a mixture of isostearic acid and coconut acid and n has an average value of 2.	surfactant - cleansing agent; surfactant - foam booster; surfactant - solubilizing agent; viscosity increasing agent - aqueous

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

Ingredient CAS No.	Definition & Structure*	Function(s)
PPG-3 Hydroxyethyl Soyamide	PPG-3 Hydroxyethyl Soyamide is the organic compound that conforms to the formula:  where RCO- represents the fatty acids derived from soybean oil and n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster; viscosity increasing agent - aqueous

*see Table 2 for available fatty acid composition

Table 2. **Fatty acid composition (%) of plant-derived fatty acid oils and of lanolin and tallow**

Fatty Acids	Brassica Campestris (Rapeseed) Seed Oil[10]	Rapeseed Acid[10]	Cocos Nucifera (Coconut) Oil[11]	Elaeis Guineensis (Palm) Oil[12]	Glycine Soja (Soybean) Oil[10]	Lanolin[13]	Tallow[14]
Caproic (C6)			0-1				
Caprylic (C8)			5-9				
Capric (C10)			6-10				
Lauric (C12)			44-52	0.2			
Myristic (C14)		≤ 0.5	13-19	1.1			3-6
Palmitic (C16)	1.5 – 3	≤ 8	8-11	44			24-32
Palmitoleic (C16:1)		≤ 2	0-1	0.1			
Stearic (C18)	0.7 - 1.3	≤ 3	1-3	4.5			20-25
Oleic (C18:1)	12.1 - 57.4	54-70	5-8	39.2	11.5 - 60.0		37-43
Linoleic (C18:2)	11.4 - 22.1	18-24	Trace-2.5	10.1			2-3
Linolenic (C18:3)	8.3 - 12.5	5-10		0.4	2.9 - 12.1		
Arachidic (C20)		≤6		0.4			
Eicosenoic (C20:1)	5.6 - 3.1						
Erucic (C22:1)	1 - 58.6						
Others		< C14 = ≤ 0.5; > C18:3 = ≤ 5; > C20 = ≤ 6				7 to 41 carbons; main fatty acids are palmitic acid (Cl6), stearic acid (Cl8), and longer molecules (C20 to C 32)	

Table 3. **Physical and Chemical Properties**

Property	Value	Reference
PEG-6 Cocamide		
Physical Form (@ 25°C)	liquid	15
Color (@ 30°C)	clear	16
Density (g/ml @ 25 ºC)	0.99	15,16
Viscosity (kg/(s x m) @ 25ºC; @ 60°C)	0.217; 0.039	16
Vapor pressure (mmHg @ 20 ºC)	0.01	15
Boiling Point (ºC)	100	15
Hydrophilic-Lipophilic Balance (HLB)	14.6	15,16
PEG-4 Rapeseedamide (60-80% purity)		
Physical Form	clear liquid	17
Color	yellow	17
Molecular Weight (g/mol)	< 600	8
Density/Specific Gravity (kg/m^3; @ 20ºC)	997	8
Vapor pressure (mm Hg)	0.0019	8
Melting Point (ºC)	5-10	8
Boiling Point (ºC)	> 262	8
Water Solubility (g/L @ 23 ºC)	9.0 x 10^{-4}	8
Other Solubility (g/L @ 20ºC)	652 – 702 in *n*-octanol	8
log K_{ow}	> 2.57 (the compound is surface active and is expected to partition to phase boundaries)	8
HLB	~11	17
PPG-2 Hydroxyethyl Cocamide		
Physical Form	liquid	7
Color	yellowish	7
Specific Gravity (@ 20 ºC)	0.98	7
Vapor pressure (mmHg 25 ºC)	5.25 x 10^{-5}	7
Boiling Point (ºC)	> 165 (decomposition occurs over the range 60 - 305)	7
Water Solubility (g/L @ 20 ºC)	< 0.001	7
log K_{ow}	0.86 to > 6.2 * (the high variability is due to the surfactant nature of this ingredient)	7

* the substance is a mixture containing different coconut acid amides of varying chain lengths, and a distribution of number of propyloxyl groups in the PPG-2 polymer

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

	# of Uses[23]	*Max Conc of Use (%)*[24]	*# of Uses*[23]	*Max Conc of Use (%)*[24]	*# of Uses*[23]	*Max Conc of Use (%)*[24]
	PEG-2 Cocamide		**PEG-3 Cocamide**		**PEG-5 Cocamide**	
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

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

	# of Uses[23]	*Max Conc of Use (%)*[24]	*# of Uses*[23]	*Max Conc of Use (%)*[24]	*# of Uses*[23]	*Max Conc of Use (%)*[24]
	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
	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[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)**[23,24]

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

*Council survey data have not yet been received for these ingredients

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	8
PPG-2 Hydroxyethyl Cocamide	Sprague-Dawley rats	5/sex	none	2000 mg/kg	24-h patch; porous gauze covered with a 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	31
				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	8
PPG-2 Hydroxyethyl Cocamide	Sprague-Dawley rats	3/sex	none specified	2000 mg/kg	by gavage (OECD TG 401)	> 2000 mg/kg	7
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	9
				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	8
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	8

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	*Salmonella typhimurium* TA1538, TA1535, TA1537, TA98, TA100	Ames test (OECD TG 471)	not mutagenic	8
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	8
PPG-2 Hydroxyethyl Cocamide	1.5 - 5000 µg/plate, with and without metabolic activation	not stated	*S. typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* CM891	Ames test (OECD TG 471)	not mutagenic	7
PPG-2 Hydroxyethyl Cocamide	with activation: 125 - 300 µg/ml initial study; 3 h); 300 -500 µg/ml (confirmation; 3 h); 450 and 500 µg/ml (confirmation 2; 3 h) without metabolic activation: 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	7
PPG-2 hydroxyethyl isostearamide (not a cosmetic ingredient; provided for read-across)	5 - 5000 µg/plate, with and without metabolic activation	DMSO	*S. typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2*uvr*A	Ames test (OECD TG 471)	not mutagenic	9
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 is 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	8
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	7

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	[8]
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	[8]
PPG-2 Hydroxyethyl Cocamide	applied neat	3 male NZW rabbits	4 h semi-occlusive 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: irritating to rabbit skin thickening of the skin, desquamation, and well-defined erythema in all 3 animals; did not resolve in 2/3 animals by day 14, with very slight erythema observed 3 min and 1 h exposure: no irritation	[33]
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 0.1 ml 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)	[34]
			HUMAN		
PEG-4 Rapeseedamide (60 - 80% pure)	0.5% aq.	50 subjects	HRIPT 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	[8]
PPG-2 Hydroxyethyl Cocamide	5% aq.	50 subjects	48 h occlusive patch; 0.2 ml 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	[7]

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

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