Safety Assessment of Alkyl Amide MIPA ingredients as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	March 15, 2019
Panel Meeting Date:	April 8-9, 2019

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 Alice Akinsulie, Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Alice Akinsulie, Scientific Analyst/Writer
Date: March 15, 2019
Subject: Safety Assessment of Alkyl Amide MIPA as used in cosmetics

Enclosed is the Draft Report on the Safety Assessment of 14 Alkyl Amide MIPA ingredients (identified as *AlkylA042019DR* in the report package). This is the first time the Panel is reviewing this document. According to the *Dictionary*, all but a few of these ingredients are reported to function in cosmetics as a surfactant or viscosity increasing agent.

According to 2019 VCRP survey data, Lauramide MIPA has the highest frequency of use, with a total of 485 formulations. Lauramide MIPA is most commonly used in bath soaps and detergents (453 formulations). Cocamide MIPA is reported to have is reported to have 335 uses, 324 of which are in rinse-off formulations.

The Council provided concentration of use survey data (identified as *AlkylA042019data1* and *AlkylA042019data2*). The results of the concentration of use survey conducted in 2017 by the Council indicate that Cocamide MIPA has the highest maximum concentration of use, and is used at up to 12% in hair bleaches. No other unpublished data were provided. Additionally, a concentration of use survey is currently being conducted by the Council on Peanutamide MIPA; once those data are received they will be incorporated into the report.

In addition to the data found in a search of the publicly available literature, comments on the SLR received from the Personal Care Products Council (Council) and have been addressed into this assessment attached herein (*AlkylA042019pcpc*).

The following are also included in this package for your review:

- *AkylA042019flow*: report flowchart
- *AlkylA042019hist*: history
- *AlkylA042019prof*: data profile
- *AlkylA042019strat*: search strategy
- *AlkylA042019FDA*: 2019 VCRP data (US FDA)

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should identify matters to be addressed in the Discussion, and then issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion. If, however, the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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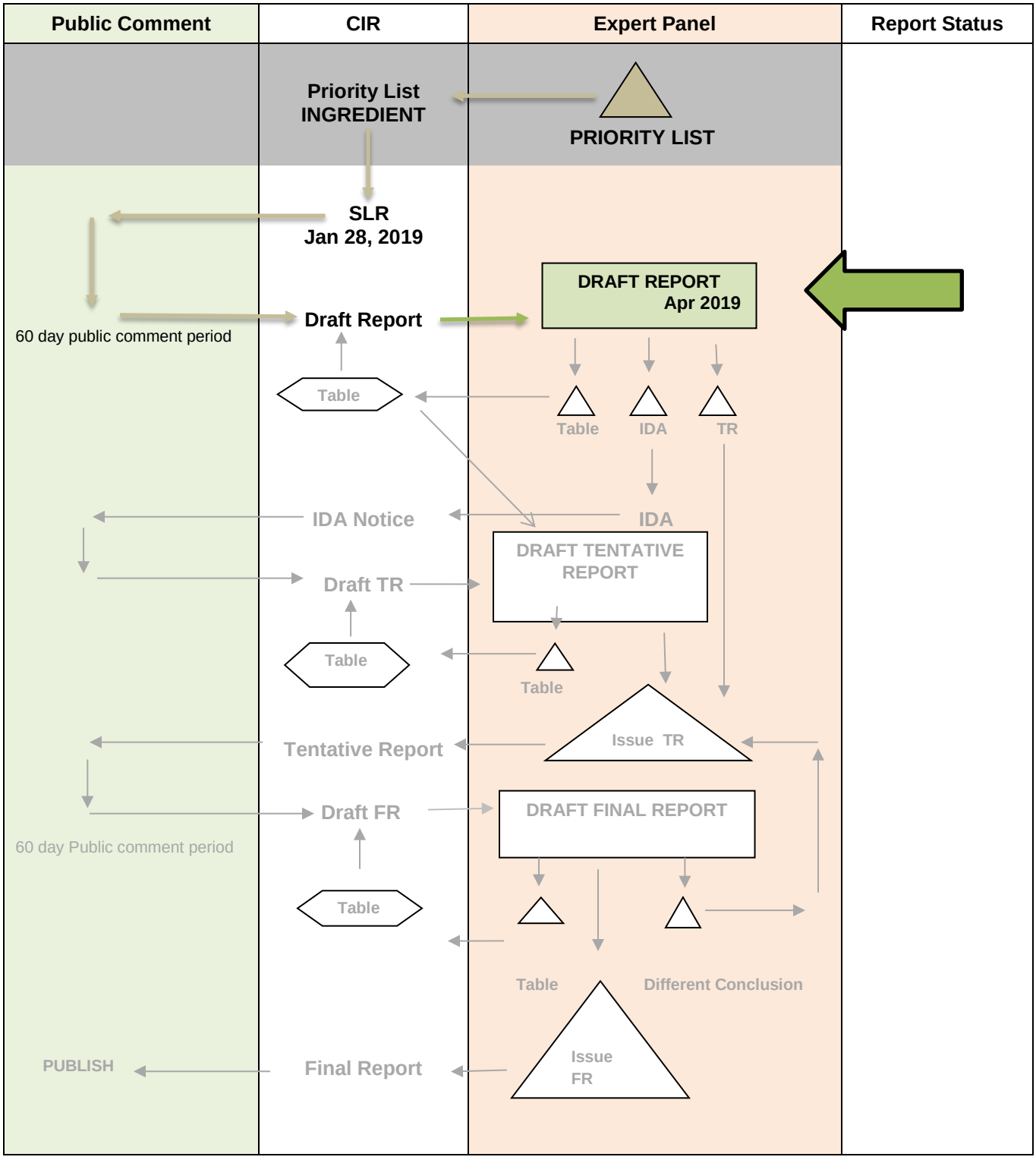
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Alkyl Amide MIPA ingredients

MEETING April 2019



Safety Assessment of Alkyl Amide MIPA ingredients as Used in Cosmetics

January 28, 2019 – Scientific Literature Review announced.

Alkyl Amide MIPA Data Profile – April 2019 – Alice Akinsulie																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Cocamide MIPA	X																												
Coconut Oil MIPA Amides																													
Hydroxyethyl Stearamide-MIPA																													
Isostearamide MIPA	X																												
Lauramide MIPA	X																												
Linoleamide MIPA																													
MIPA- Myristate																													
Myristamide MIPA																													
Oleamide MIPA	X						X	X		X	X			X	X				X				X				X		
Palmamide MIPA																													
Palm Kernelamide MIPA																													
Peanutamide MIPA																													
Ricinoleamide MIPA																													
Stearamide MIPA																													

* "X" indicates that data were available in a category for the ingredient

Alkyl Amide MIPA

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Lauramide MIPA	142-54-1	✓	3/27		✓		✓													
Cocamide MIPA	68333-82-4	✓	0/10		✓		✓													
Coconut Oil MIPA Amides	68333-82-4	✓	0/3		✓		✓													
Hydroxyethyl Stearamide-MIPA	----	✓	0/16				✓													
Isostearamide MIPA	152848-22-1	✓	2/19		✓		✓													
Linoleamide MIPA	----	✓	N/A		✓		✓													
Myristamide MIPA	10525-14-1	✓	2/12		✓		✓													
Oleamide MIPA	111-05-7 54375-42-7	✓	3/55		✓		✓	✓												
Palmamide MIPA	----	✓	N/A				✓													
Palm Kernelamide MIPA	----	✓	N/A				✓													
Peanutamide MIPA	____	✓	N/A				✓													
Ricinoleamide MIPA	40986-29-6	✓	0/5				✓													
Stearamide MIPA	35627-96-4	✓	1/9		✓		✓													
MIPA- Myristate	----	✓	N/A				✓													

Search Strategy
Relevant/total hits

PubMed
Lauramide MIPA = 0 hits; 142-54-1= 0 hits; N-(2-hydroxypropyl)dodecanamide = 0 hits; 2-Hydroxypropyllauramide = 0 hits
Cocamide MIPA = 0 hits; 68333-82-4 = 0 hits; cocamide monoisopropanolamide = 0/24 hits
Coconut Oil MIPA Amides = 0 hits; 68333-82-4 = 0 hits; Cocos Nucifera (Coconut) Oil Isopropanolamine toxicity = 0 hits
Hydroxyethyl Stearamide-MIPA = 0/12267
Isostearamide MIPA = 0/115 hits; 152848-2-1 = 0 hits ; N-(2-Hydroxypropyl)Isooctadecanamide = 0/48 hits
Linoleamide MIPA = 0 hits; Linoleoyl Monoisopropanolamide toxicity = 0/23 hits; Linoleoyl Monoisopropanolamide dermal = 0/3 hits
Myristamide MIPA = 0/34 hits; 10525-14-1 = 0 hits; Monoisopropanolamine Myristic Acid Amide = 0 hits
Oleamide MIPA = 0 hits; 111-05-7 = 0 hits; 54375-42-7 = 0 hits; Monoisopropanolamine Oleic Acid Amide = 0 hits; N-(2-hydroxypropyl)oleamide = 0 hits
Palmamide MIPA = 0/115 hits Palm Oil Acid monoisopropanolamine = 0 hits
Palm Kernelamide MIPA = 0 hits; N-(2-Hydroxypropyl)Palm Kernel Oil Acid Amide = 0 hits
Ricinoleamide MIPA = 0/81 hits; 40986-29-6 = 0 hits; 9-Octadecenamide, 12-hydroxy-N-(2-hydroxy-1-methylethyl)- = 0 hits;
Stearamide MIPA = 0 hits; Monoisopropanolamine Stearic Acid Amide = 0 hits; N-(2-Hydroxypropyl)stearamide = 0 hits;
All terms also searched in google

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- additional terms will be used as appropriate

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org

- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/

- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

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INTRODUCTION

The safety of the following 14 alkyl amide MIPA ingredients as used in cosmetics is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment. These ingredients are mixtures comprising isopropanolamides of fatty acids. 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 or viscosity increasing agent (Table 1).[1] The ingredients included in this safety assessment are:

Cocamide MIPA
Coconut Oil MIPA Amides
Hydroxyethyl Stearamide-MIPA
Isostearamide MIPA
Lauramide MIPA
Linoleamide MIPA
Oleamide MIPA
MIPA- Myristate
Myristamide MIPA
Palmamide MIPA
Palm Kernelamide MIPA
Peanutamide MIPA
Ricinoleamide MIPA
Stearamide MIPA

The rationale for this grouping of alkyl amide monoisopropanolamine (MIPA) ingredients stems from the fact that each of the ingredients in this report is a mixture of isopropanolamides of a simple carboxylic acid. (According to the *Dictionary*, MIPA is a technical name for isopropanolamine.) These ingredients are classic surfactants and viscosity increasing agents.

Diisopropanolamine, triisopropanolamine, and isopropanolamine are structurally similar to the ingredients currently under review, and are mixed aliphatic amines of isopropyl alcohol. An earlier safety assessment by the Cosmetic Ingredient Review (CIR) Expert Panel addressed the safety of diisopropanolamine, triisopropanolamine, isopropanolamine, and mixed isopropanolamine, and concluded that these ingredients are "safe as cosmetic ingredients in the present practices of use and concentration. The Panel also concluded that those ingredients should not be used in products containing *N*-nitrosating agents."[2] In 2001, the Panel considered new studies, along with updated information regarding types and concentration of use of diisopropanolamine, triisopropanolamine, and isopropanolamine. The Panel reaffirmed the conclusion and determined not to reopen the safety assessment.[3] Several components of the alkyl amide MIPA ingredients have also been reviewed.[2-14, 15] The conclusions of these reviews are provided in Table 2.

Table 2. CIR Conclusions of Components of the Alkyl Amide MIPA Ingredients that were Previously Reviewed

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 in this report were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by companies as part of the REACH chemical registration process on Oleamide MIPA.[16] When appropriate, information from these summary documents has been included in this report, and is cited to these sources.

CHEMISTRY

Definition and Structure

The definitions and structures of the alkyl amide MIPA ingredients included in this report are provided in Table 1. The available fatty acid compositions for the oils that are components of ingredients in this report are found in Table 3. The ingredients reviewed in this report are the fatty amides resulting from the amidation of fatty acids with MIPA.

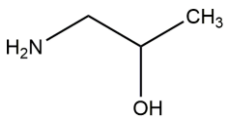


Figure 1. MIPA

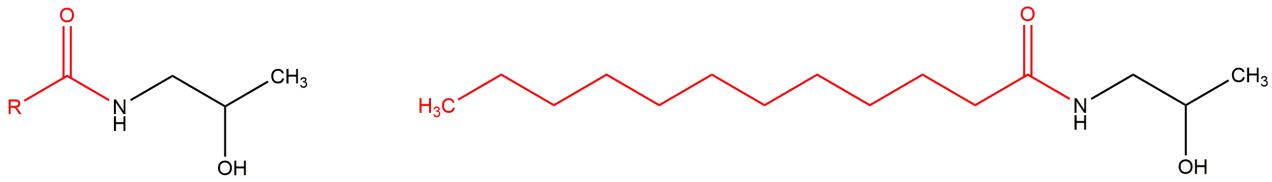


Figure 2. Alkylamide MIPA ingredients (generic) and an example (Lauramide MIPA)

However, two ingredients in this group deviate from this structure pattern. One is further substituted at MIPA (Figure 3), while the other is the MIPA salt of a fatty acid (Figure 4). Specifically, Hydroxyethyl Stearamide-MIPA is substituted with 2-ethanol. MIPA-Myristate, on the other hand, is the MIPA salt of myristic acid. MIPA-Myristate would be the direct amidase metabolite of Myristamide MIPA.

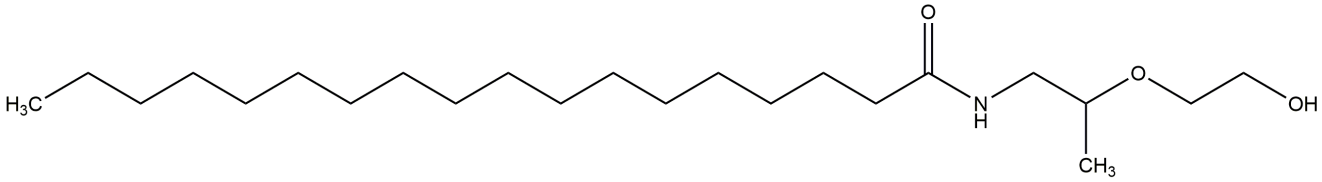


Figure 3. Hydroxyethyl Stearamide-MIPA

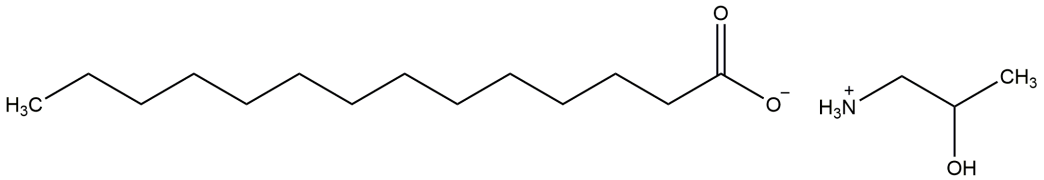


Figure 4. MIPA-Myristate

Physical and Chemical Properties

Experimental boiling point, density, vapor pressure, solubility, and log K_{ow} values were available for Lauramide, Myristamide, Oleamide, Lauramide, Ricinoleamide, and Stearamide MIPA. The available physical and chemical properties of many of the amides in this report are provided in Table 4.

Method of Manufacture

Method of manufacture data were not found in the published literature, and unpublished data were not submitted.

Impurities

Impurities data were not found in the published literature, and unpublished data were not submitted.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA 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.

The alkyl amide MIPA ingredients are primarily used in rinse-off formulations, with a few leave-on formulations. Most of the reported uses are in some type of hair or skin cleansing formulation. According to 2019 VCRP survey data, Lauramide MIPA has the highest frequency of use, with a total of 485 formulations.[17] Lauramide MIPA is most commonly used in bath soaps and detergents (453 formulations). Cocamide MIPA is reported to have is reported to have 335 uses, 324 of which are in rinse-off formulations. The results of the concentration of use survey conducted in 2017 by the Council indicate that Cocamide MIPA has

the highest maximum concentration of use, and is used at up to 12% in hair bleaches.[18] The next highest reported maximum concentration of use is 4.8% Lauramide MIPA in bath soaps and detergents. Oleamide MIPA was reported to be used in hair dyes and colors only according to VCRP data; however, the only concentration of use reported in the Council survey was in face and neck products (up to 0.4%). The highest concentration of use reported for products resulting in leave-on dermal exposure is 1% Cocamide MIPA in body and hand preparations. The use information for the alkyl amide MIPA ingredients is provided in Table 5. The ingredients not in use, according to both 2019 VCRP data and the industry survey, are listed in Table 6.

A few of the ingredients included in this safety assessment are reported to be used in products that come into contact with mucous membranes. For example, Lauramide MIPA is used in bath soaps and detergents at up to 4.8%, and Cocamide MIPA is used in bath soaps and detergents at up to 4%.[18] Additionally, a concentration of use survey is currently being conducted by the Council on Peanutamide MIPA, and once those data are received they will be incorporated into the report.

Of the 14 alkyl amide ingredients named in the report, 13 are listed in the European Union inventory of cosmetic ingredients without restrictions. MIPA- Myristate is listed by the European Commission in Annex III Part 1: the list of substances which cosmetic products must not contain, except subject to the restrictions and conditions laid down.[19] These ingredients are allowed a maximum secondary amine content of 0.5% in finished product; are not to be used with nitrosating agents; must have a minimum purity of 99%; the maximum secondary amine content of 0.5% is allowed for raw materials; maximum nitrosamine content allowed is 50 µg/kg; and the chemicals must be kept in nitrite-free containers.

Non-Cosmetic

In the US, MIPA is allowed as an indirect food additive as a component of adhesives [21 CFR 175.105] and as a defoaming agent used in the manufacture of paper and paperboard. [21CFR176.210]

TOXICOKINETIC STUDIES

Toxicokinetics studies were not found in the published literature, and unpublished data were not submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Oleamide MIPA

The acute dermal toxicity of Oleamide MIPA was determined using five female and five male Sprague-Dawley rats.[16] Rats were dermally administered 2000 mg/kg of Oleamide MIPA. The application site was covered by a semiocclusive dressing for 24 hours. Each animal was observed for 15 days after treatment. In females, moderate to severe erythema was noted at the application site in 3/5 females on day 2. Well-defined erythema was observed in 5/5 females from day 2 or 3 until day 5, which turned into very slight erythema in 3/5 females on day 6 and in 2/5 females from day 6 until day 8. A slight dryness of the skin was also noted at the application site in 5/5 females from day 3 until day 6 or 7. In males, well-defined or very slight erythema was noted at the application site of all males, from day 2 up to day 6. No unscheduled deaths occurred during the study and no clinical signs indicative of systemic toxicity were observed in any animals. The dermal LD_{50} of the test article was > 2000 mg/kg in rats.

Oral

Oleamide MIPA

An acute oral toxicity study was performed according to Organization for Economic Cooperation and Development (OECD) test guideline (TG) 423.[16] Oleamide MIPA in corn oil was administered once by gavage to two groups of three female Sprague-Dawley rats at a dosage-volume of 10 mL/kg. All animals were observed for 15 days after treatment. All animals survived until study termination. A lower body weight gain was noted in 1/6 females between days 1 and 8 and in 2/6 females between days 8 and 15. In addition, an overall lower body weight gain was observed in 1/6 females between days 1 and 15. There were no macroscopic post-mortem observations. No evidence of toxicity was observed. The oral LD_{50} of the test article was > 2000 mg/kg.

Subchronic Toxicity Studies

Oleamide MIPA

The subchronic toxicity of Oleamide MIPA was studied in a Good Laboratory Practice (GLP)-compliant study performed in accord to OECD TG 408.[16] Oleamide MIPA diluted in corn oil was administered by gavage to groups of male and female Sprague-Dawley rats (10/sex/dose) at the dose levels of 0, 100, 300, 1000 mg/kg bw/day for 13 weeks (at constant administration volume of 5 mL/kg bw). Mortality observed during the study was treatment-related. Five animals died during the study, specifically, two males of the 300 mg/kg group (days 59 and 88), and two males (days 59 and 80) and one female (day 91) of the 1000 mg/kg group. Additionally, one male of the 100 mg/kg group was killed on day 77. On the days before death, there were no

particular clinical signs but on the day of the death, decedent animals treated with 300 mg/kg showed increased salivation and absence of spontaneous locomotor activity in male. In another male, there was blood around and in the mouth. At 1000 mg/kg, there were increased salivation, chromodacryorrhea, dyspnea, bradypnea, absence of locomotor activity in male and increased salivation in female. At 100 mg/kg and at 300 mg/kg in females, there was no change in blood chemistry parameters. There was a higher creatinine level in the urine of male treated with the test article at 100 mg/kg. There was statistically significant higher plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities in the males treated with 300 and 1000 mg/kg and a statistically significant higher ALT activity in females treated at 1000 mg/kg. There was higher liver weight noted in males and females and higher adrenals weight/lower thymus weight in males treated with 1000 mg/kg of the test article. There was no other change in organ weight in animals treated at 300 or at 100 mg/kg and no mortality in the control group. The no-observed-adverse-effect-level (NOAEL) was not determined in males. In females, the NOAEL corresponds to 300 mg/kg.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oleamide MIPA

In an oral developmental toxicity study performed in accord with OECD TG 414, Oleamide MIPA diluted in corn oil was administered by gavage to groups of mated female Sprague-Dawley rats (20 mated females/dose) at dose levels of 0, 100, 300, and 1000 mg/kg bw/day from days 6 to 19 of gestation.[16] On day 20 of gestation, all mated females were killed and necropsied, and all fetuses were examined. The clinical signs (increased salivation and chromodacryorrhea) observed were at low incidence and were not attributed to a toxicological effect of the test article. The test article did not induce any relevant changes in fetuses examined at skeletal and visceral examination. There was a statistically significant lower placenta weight in the group receiving 100 mg/kg of the test substance. This was low in amplitude and was not attributed to a toxicological effect of the test substance. The NOAEL for embryo fetal development was 1000 mg/kg bw/day.

In an oral reproductive study performed in accord with OECD guideline 422, Oleamide MIPA in corn oil was administered daily by gavage to groups of 10 male and 10 female Sprague-Dawley rats.[16] In males, the test article was administered 2 weeks before mating, during the mating period, and until sacrificed (at least 5 weeks in total). Females were treated 2 weeks before mating, during the mating period (1 week), during pregnancy, during lactation until day 5 post-partum (inclusive) and until sacrificed. Animals were treated at dose-levels of 0, 100, 300, or 1000 mg/kg/day. A constant dosage-volume of 5 mL/kg/day was used. At 100 mg/kg/day, the only finding was ptyalism in most test animals. At 300 mg/kg/day, ptyalism, hypoactivity, loud breathing, piloerection and/or round back was also noted with comparable incidence. At 1000 mg/kg/day, the main clinical sign noted was ptyalism in all test animals. Hypoactivity, loud breathing, piloerection and/or round back were also recorded transiently in a few animals. No effects in the study were considered to be adverse. The NOAEL for parental toxicity, reproductive performance (mating and fertility) and toxic effects on progeny was 1000 mg/kg/day.

GENOTOXICITY

In Vitro

Oleamide MIPA

In an Ames test to examine the mutagenic activity of Oleamide MIPA in ethanol, five *Salmonella typhimurium* strains, TA1535, TA1537, TA98, TA100, and TA102, were tested with and without metabolic activation, in three or four independent assays.[16] All strains were tested with concentrations of up to 5000 µg/plate without metabolic activation. With metabolic activation, strain TA1535 was exposed to up to 500 µg/plate, and strains TA100 and TA102 were exposed to up to 5000 µg/plate. Under these experimental conditions, no mutagenic activity was revealed.

Assays testing the cytogenetic potential of Oleamide MIPA were performed with a chromosome aberration study using human lymphoblastoid cells (TK6) in accordance with OECD guideline 487.[16] Oleamide MIPA was dissolved in ethanol and tested at the highest dose compatible with the toxic activity in three assays with and without S9-mix. Using a 3-hour treatment and 27-hour recovery period, 0.05 – 0.20 mM of the test article was treated without S9-mix. In the second assay with S9-mix, 0.075 – 0.40 mM of Oleamide MIPA was tested. With 27 hours continuous treatment and no recovery period 0.0031 – 0.075 mM Oleamide MIPA was evaluated without S9-mix. Two thousand mononucleated cells were evaluated per concentration and appropriate positive controls were used. Oleamide MIPA induced no biologically or statistically significant increase in the micronucleated cells with or without metabolic activation.

A gene mutation assay was performed with Oleamide MIPA using L5178Y mouse lymphoma cells in accord with OECD TG 476.[16] Oleamide MIPA dissolved in ethanol and without S9-mix was evaluated at doses of 0.056 – 0.150 mM in a 3-hour treatment. In the second assay using a 24-hour treatment, doses of 0.020 – 0.080 mM were evaluated without metabolic activation. In another assay tested with S9-mix, doses of 0.075 – 0.3 mM were evaluated in assay 1 and doses of 0.075 – 0.175 in assay 2. Appropriate positive controls were used with and without S9-mix. In the second assay using a 3-hour treatment with metabolic activation, a statistically significant increase in the mutation frequency of total induced mutants (small and large colonies) was

noted at a concentration of 0.163 mM. Negative results were reported in the second assays studied and Oleamide MIPA was considered non-mutagenic under the conditions of this test.

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not provided.

DERMAL IRRITATION AND SENSITIZATION

Irritation

In Vitro

The primary skin irritation potential of Oleamide MIPA was evaluated using the Episkin™ reconstructed human epidermis model based on OECD TG 439.[16] The test material (undiluted Oleamide MIPA; 10 mg) was applied to skin tissue. Oleamide MIPA was considered to be non-irritant to skin.

Sensitization

Animal

The sensitization potential of Oleamide MIPA was evaluated in a guinea pig maximization study.[16] The test group consisted of 10 male and 10 female Dunkin Hartley guinea pigs, and a group of 5 males and 5 females was used as the control group. For the test group, 10% Oleamide MIPA in corn oil was used for intradermal induction (day 1), and 75% Oleamide MIPA in ethanol/water was applied for the topical induction with an occlusive dressing for 48 hours (day 8). On day 22, challenge consisted of a topical application of 50% Oleamide MIPA in acetone to the right flank and acetone to the left flank held in place by an occlusive dressing for 24 hours. The control group was administered vehicle only. Oleamide MIPA induced delayed contact hypersensitivity in more than 30% of the animals.

OCULAR IRRITATION STUDIES

In Vitro

The ocular irritation potential of Oleamide MIPA was evaluated in a bovine corneal opacity and permeability (BCOP) test performed in accord with OECD TG 437.[16] The test material (750 µL) at a concentration of 10% (w/v) in the water was applied to three corneas for 10 minutes and rinsed following application. No notable opaque spots or irregularities were observed on corneas following the treatment. The in vitro irritancy score (IVIS) was calculated as 2.0 and Oleamide MIPA was not considered an ocular corrosive or severe eye irritant under the conditions of the test.

Animal

Three male New Zealand White rabbits were used to determine the ocular irritation potential of Oleamide MIPA.[16] A dosage volume of 0.1 mL of undiluted test article was instilled into the conjunctival sac of the left eye of each rabbit, and the eyes were not rinsed. The right eye remained untreated and served as control. The mean scores (calculated using the 24, 48, and 72-h scores for each animal) for the conjunctiva ranged from 0.3 - 1.0 for redness and 0 - 0.3 for chemosis. Corneal opacity and iridial inflammation were not observed. The test substance was non-irritant when administered by ocular route to rabbits.

SUMMARY

This is a safety assessment of 14 alkyl amide MIPA ingredients as used in cosmetics. These ingredients consist of a fatty acids amidated with MIPA. The ingredients in this report are primarily reported to function as surfactants or viscosity increasing agents.

Four of the 14 ingredients included in this assessment are reported to be in use. According to 2019 VCRP data, Lauramide MIPA has the highest reported frequency of use (485 formulations), and Cocamide MIPA has the second greatest reported number of uses (335). The alkyl amide MIPA ingredients are primarily used in rinse-off formulations, and most of these reported uses are in some type of hair or skin cleansing formulations. Cocamide MIPA has the highest concentration of use, at 12% in hair bleaches. Lauramide MIPA has the next highest reported concentration of use; it is used at 4.8% in bath soaps and detergents. The highest concentrations of use reported for products resulting in leave-on dermal exposure is 1% Cocamide MIPA in body and hand preparations. Of the 14 alkyl amide ingredients named in the report, 13 are listed in the European Union inventory of cosmetic ingredients without restrictions. MIPA-Myristate is on the list of substances which must not form part of the

composition of cosmetic products, except subject to restrictions and conditions laid down. These restrictions include a maximum secondary amines contaminant content of 0.5% in finished products, a maximum secondary amines content of 0.5% in raw materials, and a maximum nitrosamine content of 50 µg/kg.

In an acute dermal toxicity study in five female and five male Sprague-Dawley rats, a single dermal application of 2000 mg/kg of Oleamide MIPA resulted in an LD_{50} > 2000 mg/kg bw. No deaths occurred during the study and no clinical signs of systemic toxicity were observed in any animals.

In an acute oral toxicity study, two groups of three female Sprague-Dawley rats were administered 2000 mg/kg Oleamide MIPA in corn oil by gavage to at a dosage-volume of 10 mL/kg. No evidence of toxicity was observed. The oral LD_{50} of the test article was greater than 2000 mg/kg.

In 13-wk oral toxicity study, 4 groups of 10 male and 10 female Sprague-Dawley rats were administered 0, 100, 300, and 1000 mg/kg bw/day Oleamide MIPA in corn oil by gavage at 5 mL/kg bw. Oleamide MIPA induced mortality, low food consumption, and low body weight gain in males. There were slight changes in the liver and the bone marrow in animals treated with test article at 1000 mg/kg. There was a higher creatinine level in the urine of male treated with the test article at 100 mg/kg and statistically significant higher plasma activities in the males treated with 300 and 1000 mg/kg and in females treated at 1000 mg/kg. The NOAEL was determined to be 300 mg/kg bw/day in females; a NOAEL was not determined for males.

A developmental toxicity test was performed with groups of 20 female rats that were dosed with 0, 100, 300, or 1000 mg/kg/day Oleamide MIPA in corn oil from days 6 to19 of gestation. The test article did not induce any relevant changes in fetuses examined at skeletal and visceral examination. There was a statistically significant lower placenta weight in the group receiving 100 mg/kg of the test substance. This was low in amplitude and was not attributed to a toxicological effect of the test substance. The NOAEL was considered to be 1000 mg/kg/day.

The reproductive toxicity of Oleamide MIPA was evaluated in groups of 10 male and female Sprague-Dawley rats at dose levels of 0, 100, 300, or 1000 mg/kg/day. In males, test article was administered 2 weeks before mating, during the mating period, and until sacrificed (at least 5 weeks in total). Females were treated 2 weeks before mating, during mating (1 week), during gestation, during lactation until day 5 post-partum (inclusive) and until sacrificed. No treatment-related, adverse effects were observed. The NOAEL for parental toxicity, reproductive performance (mating and fertility), and toxic effects on progeny was 1000 mg/kg/day.

The genotoxic potential of Oleamide MIPA was evaluated by means of an Ames test in five *S. typhimurium* strains (TA1535, TA1537, TA98, TA100, and TA102) tested either in presence or in absence of metabolic activation. Oleamide MIPA, evaluated at doses of 5 - 5000 µg/plate, was not mutagenic.

The genotoxic activity of Oleamide MIPA was assessed by means of the in vitro micronucleus test in presence and in absence of metabolic activation. TK6 lymphoblastoid human cells treated, at doses of 0.20 – 0.05 mM, were evaluated using a 3-hour treatment and 27-hour recovery period without s9-mix. Using a 3-hour treatment and 27-hour recovery period 0.20 – 0.05 mM of the test article was evaluated without S9-mix. In the second assay with S9-mix (5% S9-mix), 0.40 –0.075 mM of Oleamide MIPA was tested. With 27 hours continuous treatment and no recovery period 0.075 – 0.0031 mM Oleamide MIPA was studied without S9-mix. Under these experimental conditions, no genotoxic activity was revealed.

The search for any mutagenic activity of Oleamide MIPA, was studied by means of gene mutation test at the TK locus in L5178Y mouse lymphoma cell culture in accord with OECD Guideline 476, in 2 independent assays performed both without and with metabolic activation. Oleamide MIPA dissolved in ethanol and without S9-mix was evaluated at doses of 0.150 – 0.056mM in a 3-hour treatment. In the second assay using a 24-hour treatment doses of 0.080 –0.020 mM was evaluated without metabolic activation. With S9-mix, doses of 0.3 – 0.075mM evaluated in assay 1 and doses of 0.175 – 0.075 in assay 2. Under these experimental conditions, the test item induced no mutagenic activity

The dermal irritation potential of undiluted Oleamide MIPA was evaluated in vitro using the Episkin™ reconstructed human epidermis model. Oleamide MIPA was determined to be a non-irritant to skin. In a guinea pig maximization test, 10% Oleamide MIPA in corn oil, 75% Oleamide MIPA in ethanol/water, and 50% Oleamide MIPA induced delayed contact hypersensitivity in more than 30% of the 20 test animals.

The ocular irritation potential of 750 µL Oleamide MIPA was evaluated using a BCOP study according to OECD TG 437. An irritancy score of 2.0 was reported and it was concluded that the Oleamide MIPA is not an ocular corrosive or severe irritant. Undiluted Oleamide MIPA was not irritating to rabbit eyes.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

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

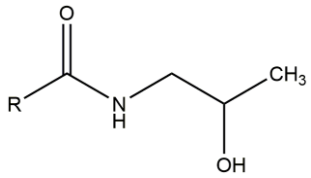
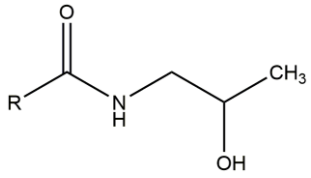
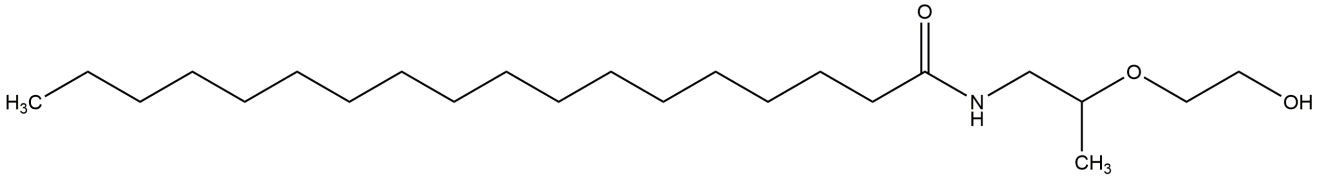
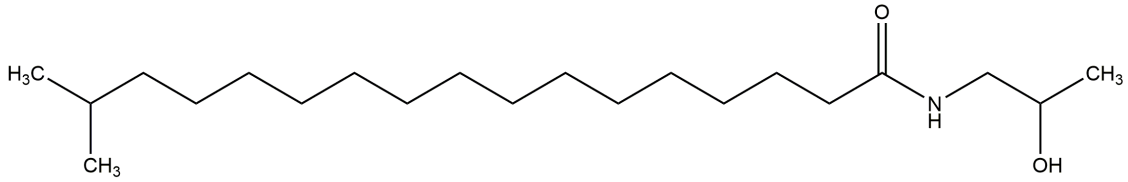
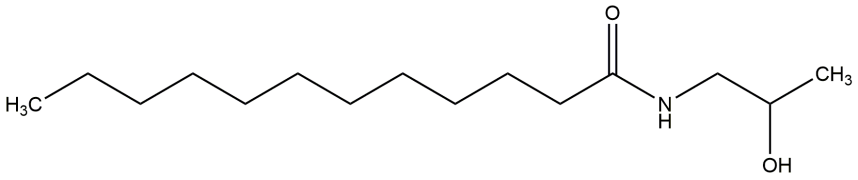
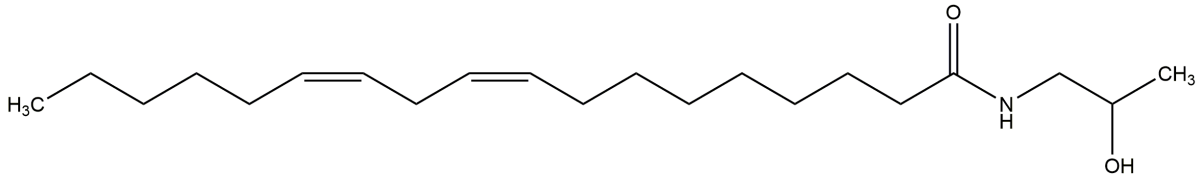
Ingredient & CAS No.	Definition & Example Structure	Function(s)
Cocamide MIPA 68333-82-4	Cocamide MIPA is a mixture of isopropanolamides of coconut acid.  wherein RC(O)- represents the fatty acid residues derived from coconut acid.	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Coconut Oil MIPA Amides 68333-82-4	Coconut Oil MIPA Amides is the mixture of amides produced by the transamidation of *Cocos nucifera* (coconut) oil with isopropanolamine.  wherein RC(O)- represents the fatty acid residues derived from coconut oil.	Viscosity Increasing Agents - Nonaqueous
Hydroxyethyl Stearamide-MIPA	Hydroxyethyl Stearamide-MIPA is the substituted isopropanolamide. 	Opacifying Agents; Viscosity Increasing Agents - Aqueous
Isostearamide MIPA 152848-22-1	Isostearamide MIPA is a mixture of isopropanolamides of isostearic acid. 	Surfactants - Foam Boosters; Viscosity Increasing Agents – Aqueous
Lauramide MIPA 142-54-1	Lauramide MIPA is a mixture of isopropanolamides of lauric acid. 	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Linoleamide MIPA	Linoleamide MIPA is a mixture of isopropanolamides of linoleic acid. 	Hair Conditioning Agents; Surfactants - Foam Boosters; Viscosity Increasing Agents – Aqueous

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

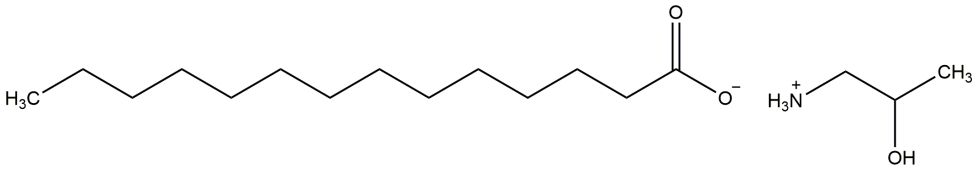
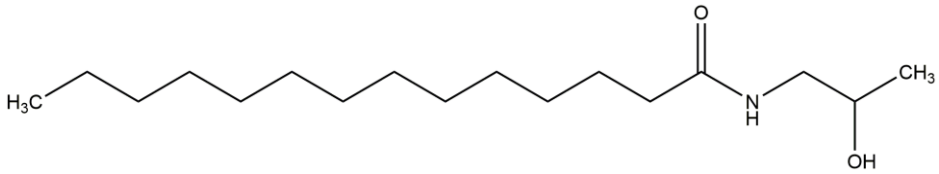
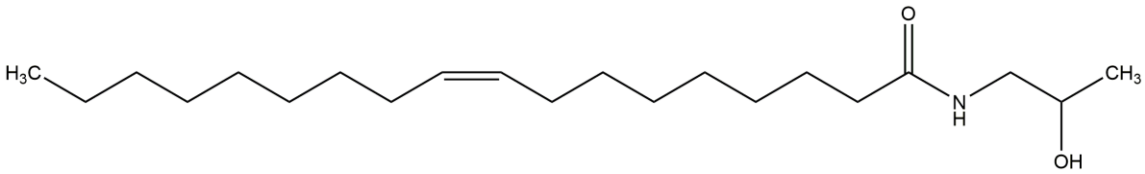
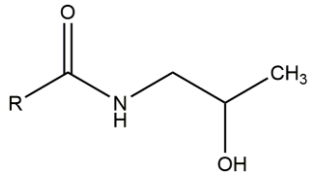
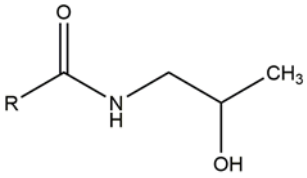
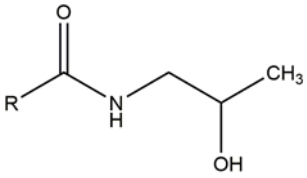
Ingredient & CAS No.	Definition & Example Structure	Function(s)
MIPA-Myristate	MIPA-Myristate is the salt of monoisopropanolamine and myristic acid. 	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Myristamide MIPA 10525-14-1	Myristamide MIPA is a mixture of isopropanolamides of myristic acid. 	Surfactants - Foam Boosters; Viscosity Increasing Agents – Aqueous
Oleamide MIPA 111-05-7	Oleamide MIPA is a mixture of isopropanolamides of oleic acid. 	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Palmamide MIPA	Palmamide MIPA is a mixture of isopropanolamides of the fatty acids derived from *Elaeis guineensis* (palm) oil.  wherein RC(O)- represents the fatty acid residues derived from *Elaeis guineensis* (palm) oil.	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Palm Kernelamide MIPA	Palm Kernelamide MIPA is a mixture of isopropanolamides of the fatty acids derived from *Elaeis guineensis* (palm) kernel oil.  wherein RC(O)- represents the fatty acid residues derived from *Elaeis guineensis* (palm) kernel oil.	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Peanutamide MIPA	Peanutamide MIPA is a mixture of isopropanolamides of the fatty acids derived from *Arachis hypogaea* (peanut) oil  wherein RC(O)- represents the fatty acid residues derived from *Arachis hypogaea* (peanut) oil.	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous

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

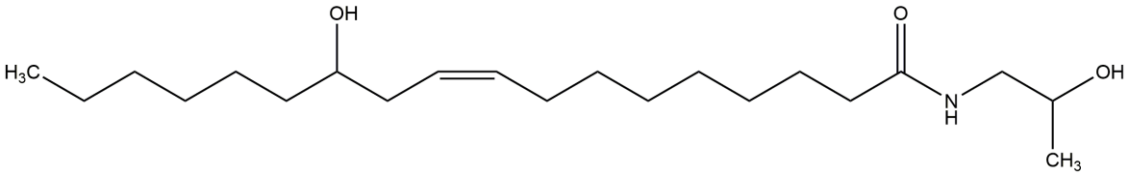
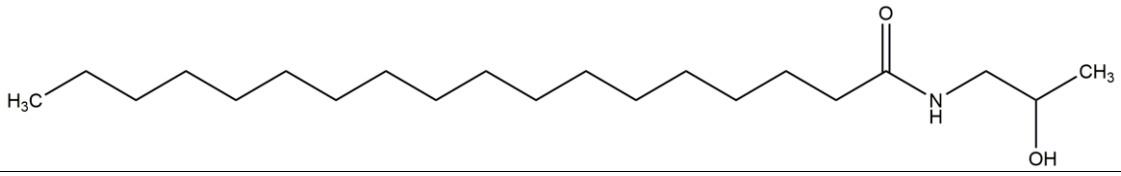
Ingredient & CAS No.	Definition & Example Structure	Function(s)
Ricinoleamide MIPA 40986-29-6	Ricinoleamide MIPA is a mixture of isopropanolamides of ricinoleic acid. 	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Stearamide MIPA 35627-96-4	Stearamide MIPA is a mixture of isopropanolamides of stearic acid. 	Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous

Table 2. CIR Conclusions of Components of the Alkyl Amide MIPA Ingredients that were Previously Reviewed

Component Reviewed	Conclusion	Assessment Publication Status	Reference
Arachis Hypogaea (Peanut) Oil	Safe as used	Published in 2001; Included in expanded report of plant-derived fatty acid published in 2017	10,15
Coconut Acid	Safe as used	Published in 1986; Re-review published in 2011; reviewed in 2017	9,10,14
Cocos Nucifera (Coconut) Oil	Safe as used	Published in 1986; Re-review published in 2011; reviewed in 2017	9,10,14
Elaeis Guineensis (Palm) Oil	Safe as used	Published in 2000 Included in expanded report of plant-derived fatty acid published in 2017	4,10
Elaeis Guineensis (Palm) Kernel Oil	Safe as used	Published in 2000 Included in expanded report of plant-derived fatty acid published in 2017	4,10
Isopropanolamine	Safe as used	Published in 1987; re-review published in 2006 – not reopened	2,3
Isostearic Acid	Safe as used	published in 1983; re-review published in 2005 – not reopened	6,12
Lauric Acid	Safe as used	published in 1987; re-review published in 2006 – not reopened	7,13
Linoleic Acid		Currently under review	11
Myristic Acid	Safe as used	published in 1987; re-review published in 2006 – not reopened; included in expanded report with salts and esters published in 2010	7,8,13
Oleic Acid	Safe as used	published in 1987; re-review published in 2006 – not reopened	7,13
Ricinoleic Acid	Safe as used	published in 2007	5
Stearic Acid	Safe as used	published in 1987; re-review published in 2006 – not reopened	7,13

Table 3. Fatty acid composition (%) of component plant-derived fatty acid oils

Fatty Acids	Cocos Nucifera (Coconut) Oil[9]	Elaeis Guineensis (Palm) Oil[4]	Elaeis Guineensis (Palm) Kernel Oil[4]
Caproic (C6)	0-1		0.3
Caprylic (C8)	5-9		4.4
Capric (C10)	6-10		3.7
Lauric (C12)	44-52	0.2	48.3
Myristic (C14)	13-19	1.1	15.6
Palmitic (C16)	8-11	44	
Palmitoleic (C16:1)	0-1	0.1	7.8
Stearic (C18)	1-3	4.5	2
Oleic (C18:1)	5-8	39.2	15.1
Linoleic (C18:2)	Trace-2.5	10.1	2.7
Linolenic (C18:3)		0.4	
Arachidic (C20)		0.4	
Others			0.2

Table 4. Physical and Chemical Properties

Property	Value	Reference
	Hydroxyethyl Stearamide-MIPA	
Molecular Weight (g/mol)	385.6	[20]
	Isostearamide MIPA	
Molecular Weight (g/mol)	341.58	[21]
	Lauramide MIPA	
Molecular Weight (g/mol)	257.418	[22]
Density/Specific Gravity (@ 20ºC)	0.919 ± 0.06	[23]
Melting Point (ºC)	65 – 66	[23]
Boiling Point (ºC)	418.3 ± 28.0	[23]
Disassociation constants pKa (@25ºC)	14.56 ± 0.20	[23]
	Linoleamide MIPA	
Molecular Weight (g/mol)	337.6	[20]
	Myristamide MIPA	
Molecular Weight (g/mol)	285.472	[24]
Molecular Volume (mL/mol)	312.9 ± 3.0	[23]
Formula Weight	303.5	[20]
Density (@ 20ºC)	0.912 ± 0.06	[23]
Vapor Pressure (@ 25ºC)	9.44 x 10^{-10}	[23]
Melting Point (ºC)	70 – 72	[23]
Boiling Point (ºC)	444.1 ± 28.0	[23]
Disassociation constants pKa (@25ºC)	14.56±0.20	[23]
	Oleamide MIPA	
Physical Form	Paste	[16]
Color	Beige	[16]
Odor	Strong	[16]
Molecular Weight (g/mol)	339.564	[25]
Density/Specific Gravity (g/mL @ 25ºC)	0.883, 0.891	[16]
Vapor pressure (25ºC)	0	[16]
Melting Point (ºC)	35.9 - 41.7	[16]
Boiling Point (ºC)	503.6 ± 43.0	[23]
Water Solubility (mg/L)	1	[16]
log K_{ow}	6.39	[16]
	Ricinoleamide MIPA	
Molecular Weight (g/mol)	355.56	[23]
Molecular Volume (mL/mol)	370.4 ± 3.0	[23]
Density (@ 20ºC)	0.959 ± 0.06	[23]
Vapor pressure (@ 25ºC)	5.15 x 10^{-14}	[23]
Boiling Point (ºC)	542.1 ± 40.0	[23]
Disassociation constants pKa (@25ºC)	14.51 ± 0.10	[23]
	Stearamide MIPA	
Molecular Weight (g/mol)	341.57	[23]

Table 4. Physical and Chemical Properties

Property	Value	Reference
Molecular Volume (mL/mol)	378.9 ± 3.0	[23]
Density (@ 20ºC)	0.901 ± 0.06	[23]
Vapor pressure (@ 25ºC)	8.03 x 10^{-12}	[23]
Boiling Point (ºC)	493.8 ± 28.0	[23]
Disassociation constants pKa (@25ºC)	14.56 ± 0.20	[23]

Table 5. Frequency and concentration of use data for alkyl amide MIPA ingredients

	# of Uses[17]	Max Conc of Use (%)[18]	# of Uses[17]	Max Conc of Use (%)[18]	# of Uses[17]	Max Conc of Use (%)[18]
	Cocamide MIPA		**Isostearamide MIPA**		**Lauramide MIPA**	
Totals*	**335**	**0.1 - 12**	**8**	**NR**	**485**	**2 - 4.8**
Duration of Use						
Leave-On	*10*	*0.12 - 1*	*NR*	*NR*	*2*	*NR*
Rinse-Off	*324*	*0.1 - 12*	*8*	*NR*	*480*	*2 - 4.8*
Diluted for (Bath) Use	*1*	*1.5 - 2*	*NR*	*NR*	*3*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	3[a]	0.12[b]	NR	NR	1	NR
Incidental Inhalation-Powder	3[a]	1[c]	NR	NR	NR	NR
Dermal Contact	162	0.1 - 4	2	NR	478	3 - 4.8
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	149	0.12 - 3.7	6	NR	7	2
Hair-Coloring	18	12	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	151	1.1 - 4	NR	NR	472	4.8
Baby Products	NR	NR	NR	NR	NR	NR

	Oleamide MIPA	
Totals*	**51**	**0.4**
Duration of Use		
Leave-On	*NR*	*0.4*
Rinse Off	*51*	*NR*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	NR	NR
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	NR	NR
Incidental Inhalation-Powder	NR	0.4[c]
Dermal Contact	NR	0.4
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	51	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR

NR = Not reported.

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

[a.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

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

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 6. Ingredients not reported to be in use (according to VCRP and Council survey data)[17,18]

Coconut Oil MIPA Amides	c
Hydroxyethyl Stearamide MIPA	
Linoleamide MIPA	
Myristamide MIPA	
Palmamide MIPA	
Palm Kernelamide MIPA	
Peanutamide MIPA (Concentration of use survey currently being conducted)	
Ricinoleamide MIPA	
Stearamide MIPA	
MIPA-Myristate	

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CATEGORY	MAINTERM	COUNT
02B - Bubble Baths	COCAMIDE MIPA	1
05E - Rinses (non-coloring)	COCAMIDE MIPA	1
05F - Shampoos (non-coloring)	COCAMIDE MIPA	146
05I - Other Hair Preparations	COCAMIDE MIPA	2
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	COCAMIDE MIPA	13
06D - Hair Shampoos (coloring)	COCAMIDE MIPA	4
06H - Other Hair Coloring Preparation	COCAMIDE MIPA	1
10A - Bath Soaps and Detergents	COCAMIDE MIPA	104
10C - Douches	COCAMIDE MIPA	6
10E - Other Personal Cleanliness Products	COCAMIDE MIPA	40
11E - Shaving Cream	COCAMIDE MIPA	1
12A - Cleansing	COCAMIDE MIPA	8
12D - Body and Hand (exc shave)	COCAMIDE MIPA	3
12J - Other Skin Care Preps	COCAMIDE MIPA	5
05F - Shampoos (non-coloring)	ISOSTEARAMIDE MIPA	6
12A - Cleansing	ISOSTEARAMIDE MIPA	1
12H - Paste Masks (mud packs)	ISOSTEARAMIDE MIPA	1
02B - Bubble Baths	LAURAMIDE MIPA	3
04E - Other Fragrance Preparation	LAURAMIDE MIPA	1
05F - Shampoos (non-coloring)	LAURAMIDE MIPA	7
10A - Bath Soaps and Detergents	LAURAMIDE MIPA	453
10E - Other Personal Cleanliness Products	LAURAMIDE MIPA	16
12A - Cleansing	LAURAMIDE MIPA	2
12H - Paste Masks (mud packs)	LAURAMIDE MIPA	2
12J - Other Skin Care Preps	LAURAMIDE MIPA	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	OLEAMIDE MIPA	51

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D., Executive Director
COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: September 28, 2017

SUBJECT: Concentration of Use by FDA Product Category: Alkyl Amide MIPA Ingredients

Concentration of Use by FDA Product Category – Alkyl Amide MIPA Ingredients*

Lauramide MIPA
Cocamide MIPA
Coconut Oil MIPA Amides
Hydroxyethyl Stearamide-MIPA
Isostearamide MIPA
Linoleamide MIPA
Myristamide MIPA
Oleamide MIPA
Palmamide MIPA
Palm Kernelamide MIPA
Ricinoleamide MIPA
Stearamide MIPA
MIPA-Myristate

Ingredient	Product Category	Maximum Concentration of Use
Lauramide MIPA	Shampoos (noncoloring)	2%
Lauramide MIPA	Bath soaps and detergents	4.8%
Lauramide MIPA	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	3%
Cocamide MIPA	Bubble baths	2%
Cocamide MIPA	Other bath preparations	1.5%
Cocamide MIPA	Shampoos (noncoloring)	1.3-3.7%
Cocamide MIPA	Tonics, dressings and other hair grooming aids	0.12%
Cocamide MIPA	Hair bleaches	12%
Cocamide MIPA	Bath soaps and detergents	1.1-4%
Cocamide MIPA	Other personal cleanliness products	3%
Cocamide MIPA	Skin cleansing (cold creams, cleansing lotions liquids and pads)	0.1-3.5%
Cocamide MIPA	Body and hand products Not spray	1%
Cocamide MIPA	Other skin care preparations Rinse-off	1.5%
Oleamide MIPA	Face and neck products Not spray	0.4%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2017
Table prepared: September 27, 2017

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 15, 2019

SUBJECT: Scientific Literature Review: Safety Assessment of Alkyl Amide MIPA Ingredients (release date January 28, 2019)

The Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Alkyl Amide MIPA Ingredients as Used in Cosmetics.

The Council has no suppliers listed for the following ingredients included in this report:

Linoleamide MIPA
Myristamide MIPA
Palmamide MIPA
Palm Kernelamide MIPA
Ricinoleamide MIPA
Stearamide MIPA
MIPA-Myristate

Key Issues

As much of the information in the report is from the ECHA dossier on Oleamide MIPA, in the Introduction, it would be helpful to indicate that a source of information was the third party summaries found in the dossier.

Additional Considerations

Introduction - Please defined MIPA in the Introduction.

Cosmetic Use - It should be made clear that the only ingredient in the CIR report associated with EU Annex III number 61 (monoalkanolamines) is MIPA-Myristate.

DART - Please indicate that the second study was an OECD 422 guideline study.

Effect on Cell Proliferation and Apoptosis, Summary - The OECD 408 guideline study is a 90-day oral study. This study should be presented in the Subchronic section, not in a separate section under other relevant studies. Although the Summary states: "There were no changes in cell proliferation and apoptosis attributed to the test article." There is no statement regarding cell proliferation and apoptosis earlier in the report. More details about the results of this study (especially about liver and bone marrow histopathologic changes) should be included in the CIR report.

Summary - The concentration tested in the guinea pig maximization study should be stated in the Summary.

Reference 8 - Please correct "dossiee"

Reference 11 - Please correct "nomoalkanolamines"

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