Safety Assessment of Alkyl Amide MIPA Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	November 15, 2019
Panel Meeting Date:	December 9-10, 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.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.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, former CIR Scientific Analyst/Writer, and Monice Fiume, Senior Director.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢
cirinfo@cir-safety.org

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons

From: Monice M. Fiume MMF
Senior Director, CIR

Date: November 15, 2019

Subject: Draft Final Report of the Safety Assessment of Alkyl Amide MIPA Ingredients

Enclosed is the Draft Final Report of the Safety Assessment of Alkyl Amide MIPA Ingredients as Used in Cosmetics. (It is identified as *aaMIPA122019rep* in the pdf document.) At its September 2019 meeting, the Panel issued a Tentative Report with the conclusion that these 14 alkyl amide MIPA ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

The ECHA data have been clarified in this version of the report, specifically in regard to substances that were provided as read-across sources. These data are incorporated into the CIR safety assessment because the Panel determined that the data that ECHA used for read-across were applicable to fulfill the data needs for the missing data endpoints on these alkyl amide MIPA ingredients. The CIR staff did not include information from the CIR report on diethanolamides in the current assessment of alkyl amide MIPA ingredients because, at the April meeting, the Panel decided to not include those data.

The information from the ECHA dossiers was captured and presented in the CIR report as given in the ECHA dossiers. However, in comments received from the Council on the Tentative Report issued by CIR, the Council remarked that

> Although the ECHA dossier does not specifically state that the 14-week and the 104-week dermal studies on "amides, C 12-18 and C 18-unsatd., -(hydroxyethyl)" are the NTP studies on Cocamide DEA, a comparison between the NTP bioassay … and the studies in the ECHA dossier indicates that they are the same. Both report using the same lot of test material, the source of the animals was the same and the dates the studies were completed were the same. Please cite these studies to the primary reference, the NTP bioassay.

Accordingly, what is the preference of the Panel? If it is to identify the test substance in those dermal studies as Cocamide DEA, should other data from the CIR report on diethanolamides be incorporated into the safety assessment of alkyl amide MIPA ingredients? For your convenience, the CIR report on diethanolamides has been included with this submission (*aaMIPA122019DEA*). (The NTP study referred to by the Council is summarized in the diethanolamides report.)

Comments on the Draft Report that were received from the Council prior to the September meeting (*aaMIPA122019pcpc_1*), as well as the comments referred to above the were received on the Tentative Report (*aaMIPA122019pcpc_2*), were addressed and are included herein. The following are also included as a part of this report package:

aaMIPA122019flow: report flowchart
aaMIPA122019hist: report history
aaMIPA122019prof: data profile
aaMIPA122019strat: search strategy
aaMIPA122019min: transcripts
aaMIPA122019FDA: 2019 VCRP data

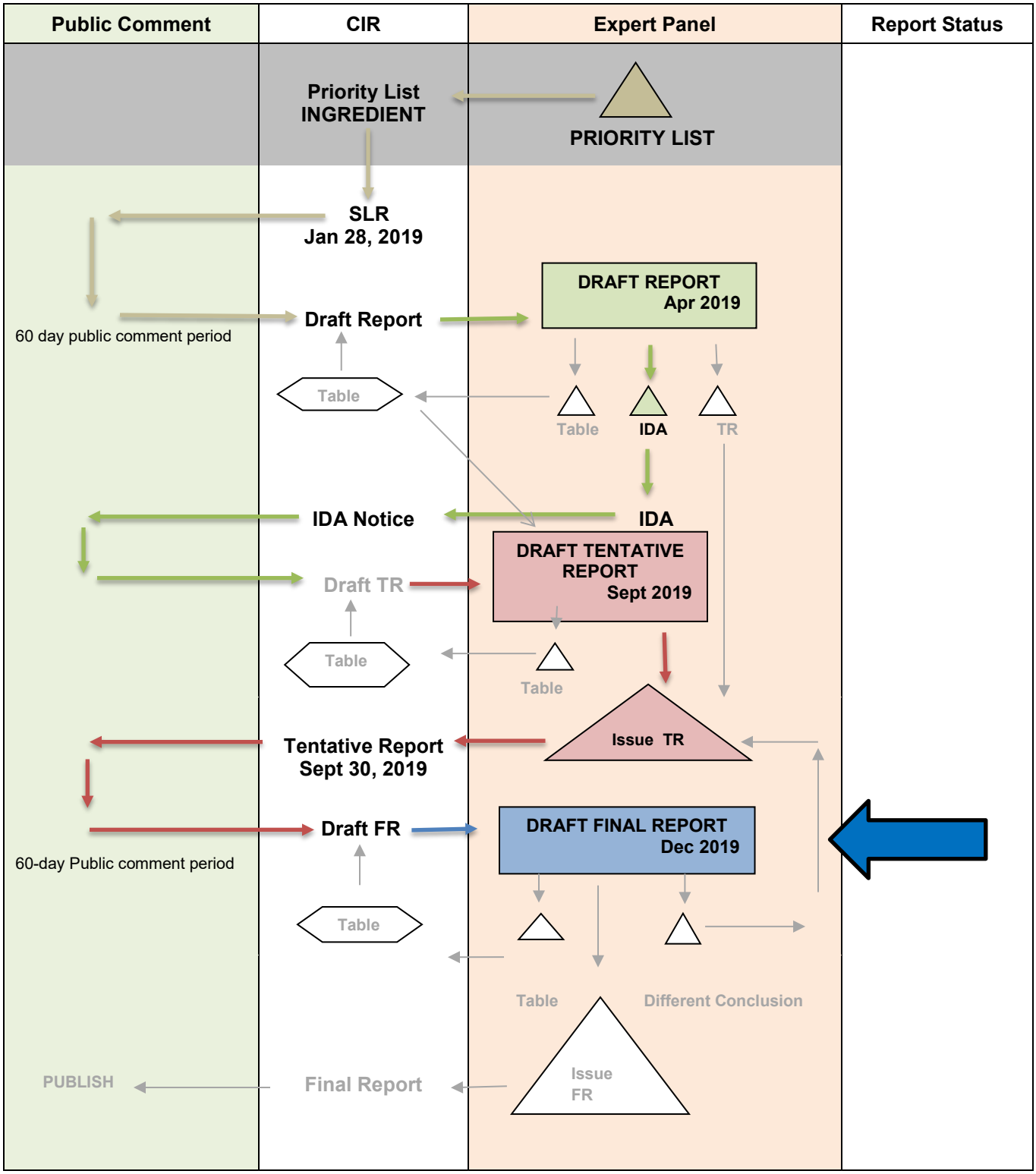
The Panel should carefully consider the Discussion, and issue a Final Report.

1620 L Street, NW, Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(email) cirinfo@cir-safety.org (website) https://cir-safety.org

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Alkyl Amide MIPA ingredients

MEETING December 2019



Safety Assessment of Alkyl Amide MIPA ingredients as Used in Cosmetics

January 28, 2019 – Scientific Literature Review announced.

April 6-7, 2019 – Draft Report

The Panel requested that the report be updated with the available REACH dossiers. The also issued an IDA requesting the following:

- skin sensitization data for Cocamide MIPA, at maximum leave-on use concentration
- skin sensitization data on other alkyl amide MIPAs, at maximum concentrations of use
- 28-day dermal toxicity study on Cocamide MIPA
    - if positive, additional data may be requested

September 16-17, 2019 – draft Tentative Report

Concentration of use data for Peanutamide MIPA; no use data were reported for this ingredient. Additionally, data were received that clarified that the reported use of 1% Cocamide MIPA in body and hand products is a rinse-off use; consequently, the highest reported leave-on dermal use concentration is 0.4% Oleamide MIPA in a face and neck formulation.

Information on Cocamide MIPA an Isostearamide MIPA included in REACH dossiers (as well as information on substances used for read-across) was added to the report.

The Panel concluded that the 14 alkyl amide MIPA ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

December 9-10, 2019 – draft Final Report

No new data were received since the Tentative Report was issued.

Alkyl Amide MIPA Ingredients Data Profile – December 2019 – Monice Fiume

				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
General Info on alkyl amide MIPAs		X	X																										
Cocamide MIPA	X		X				X	X		RA	RA		RA	RA	X		RA			RA			X				RA		
Coconut Oil MIPA Amides																													
Hydroxyethyl Stearamide-MIPA																													
Isostearamide MIPA	X						X	X		RA	X		RA	RA	X	X	RA			X			X				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																													
Cocamide MIPA, via read-across:																													
amides, C8-18 and C18-unsatd., *N*-(hydroxyethyl)							X													X							X		
amides, C12-18 and C18-unsatd. *N*-(hydroxyethyl)											X																		
Cocamide MIPA and Isostearamide MIPA, via read-across:																													
amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl)										X			X																
amides, C12-18 (even-numbered) and C18-unsatd., *N,N*-bis(hydroxyethyl)														X	X		X												

* "X" indicates that data were available in a category for the ingredient
RA – see read-across information

Alkyl Amide MIPA

Ingredient	CAS #	InfoB	SciFin	TOXNET	FDA	EU	ECHA	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH
Cocamide MIPA	68333-82-4	✓	0/10	1/2		✓	yes	no	no	no		no			
Coconut Oil MIPA Amides	68333-82-4	✓	0/3	1/2		✓		no	no	no		no			
Hydroxyethyl Stearamide-MIPA	----	✓	0/16			✓		no	no	no		no			
Isostearamide MIPA	152848-22-1	✓	2/19	1/1		✓	yes	no	no	no		no			
Lauramide MIPA	142-54-1	✓	3/27	1/2		✓	preR	no	no	no		no			
Linoleamide MIPA	----	✓	N/A	0		✓	no	no	no	no		no			
MIPA- Myristate	----	✓	N/A			✓	no	no	no	no		no			
Myristamide MIPA	10525-14-1	✓	2/12	1/1		✓		no	no	no		no			
Oleamide MIPA	111-05-7 54375-42-7	✓	3/55	✓		✓	✓	no	no	no		no			
Palmamide MIPA	----	✓	N/A			✓	no	no	no	no		no			
Palm Kernelamide MIPA	----	✓	N/A			✓	yes/?	no	no	no		no			
Peanutamide MIPA	-----	✓				✓	no	no	no	no		no			
Ricinoleamide MIPA	40986-29-6	✓	0/5			✓	no	no	no	no		no			
Stearamide MIPA	35627-96-4	✓	1/9	✓		✓	preR	no	no	no		no			

Search Strategy

PubMed - *results are updated weekly*

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;

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)

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/
- 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/

APRIL 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

BELSITO TEAM – April 8, 2019

DR. BELSITO: Alkyl Amide MIPA. So this is also the first time we're looking at these, right?

DR. SNYDER: Mm-hmm.

DR. BELSITO: And we've gotten some Wave 2 data. So I guess the question I had was Cocamide MIPA and Coconut Oil MIPA Amides, how did they differ? Bart, can you tell me?

And then I also had a question for Dan and, I guess, Bart about Hydroxyethyl Stearamide-MIPA and MIPA-Myristate. Do they belong in these groups, particularly, the MIPA-Myristate, just looking at the chemical structure? The Hydroxyethyl Stearamide-MIPA has this different tail, as does the MIPA-Myristate. I mean, they just look different to me. I'm not a chemist. I'm on page 12 of the PDF.

DR. HELDRETH: So for your question about the two coconut ingredients, at least based on the INCI definition, it seems that the method of manufacture for the two are different. However, the end result is probably not very different. But in the definition --

DR. BELSITO: Okay. But there are two different names in the dictionary, so we include both of them in the report. Is that the way it goes?

DR. HELDRETH: Right. So for the Cocamide MIPA, it says it's derived from the coconut acid and they're amidating the coconut acid; whereas, as in the coconut oil MIPA amides, they're starting with coconut oil. So they're talking mostly the triglycerides that are going to have to be essentially trans-amidated.

DR. BELSITO: Okay.

DR. HELDRETH: But the end result should be a very similar distribution of chain links.

DR. BELSITO: Okay.

DR. LIEBLER: So I was okay with all the ingredients.

DR. BELSITO: Okay.

DR. LIEBLER: Is that what you're --

DR. BELSITO: Yeah, so I just had a question about the page PDF 12, Figures 3 and 4 for Hydroxyethyl Stearamide-MIPA and MIPA-Myristate. They look so different to me.

DR. LIEBLER: Yeah, one is the salt and one's an amide. One is essentially -- well, one is similar -- the bottom one, the MIPA-Myristate, is like a hydrolysis product of the upper structure, although they're not the exact same precursor in hydrolysis product, but it's the same thing. And you would expect these to be hydrolyzed in vivo to some extent, particularly, if absorbed orally.

So the MIPA-Myristate, that's the only one that could be considered different in this report because, essentially, you're talking about a salt that's incorporated to a cosmetic ingredient. And those two pieces, the carboxylic acid and the MIPA piece, are going to not just be bound to each other. They're not going to be next to each other; they're going to be complex with whatever else is in the formulation.

And so it's essentially the equivalent of having myristic acid because it's a weak acid. It will protonate mostly. It would be myristic acid. And the MIPA will also – it will actually mostly be protonated in most neutral PH formulas.

DR. BELSITO: So does it belong there?

DR. LIEBLER: Is the use similar for that one?

DR. SNYDER: They're all surfactants, aren't they?

DR. LIEBLER: It doesn't have any distinct different use, or do we know?

DR. HELDRETH: It's a surfactant, foam booster, viscosity increasing agent.

DR. LIEBLER: Yeah.

DR. HELDRETH: So it falls in with the rest. I mean, the actual amide version of that Myristamide MIPA is a surfactant, foam booster, viscosity increasing agent.

DR. LIEBLER: Yeah, I mean, I think having all the amides in -- it's a no-brainer for all of the amides. The MIPA-Myristate is a solid myristic acid in MIPA. I think because of the MIPA part, it does belong in the report. It's going to have, essentially, the same kind of toxicology considerations, the same kind of risks for skin sensitization, irritation, and it's going to have probably similar absorption.

So I think you could argue that because it's salt and not the ester, it doesn't belong in this strictly based on chemistry. And I think I would argue that it doesn't belong anywhere else by itself. So that's why I think it belongs in this report.

DR. SNYDER: So my question was all of the tox data is on the Oleamide?

MS. AKINSULIE: Yes.

DR. SNYDER: And then in the subchronic study, there was not a NOAEL for the males, and there was liver weight and bone marrow effects. And the repro is on the Oleamide and the NOAEL was at the highest dose tested. But so what about the read across for all of these if we only have data on Oleamide?

And so it's kind of driven by the fact that we think there's going to be dermal absorption -- and because we do have some evidence of toxicity and the subchronic study. We don't have a NOAEL for the males. So it went all the way down to the lowest dose tested, which was 100 milligrams per kilogram in an oral study.

DR. BELSITO: I have a comment about that. Again, my comments aren't linked. I don't know why.

DR. SNYDER: So I think we need absorption data on all of them.

DR. BELSITO: So what they found in the male, though, was increased salivation in absence of spontaneous locomotor activity, which is why they didn't have a NOAEL in the repro.

DR. SNYDER: No, in the repro, they've got NOAEL. A thousand, the highest dose tested, in the subchronic. That's the subchronic --

DR. BELSITO: Subchronic. Okay. Yeah, so increased salivation in absence of --

DR. SNYDER: That's not what drove it. It was liver enzyme increases and increased liver weights, and there were deaths. If you go back to the beginning, there were a number of deaths, all the way down to a 100 in the males. Mortality was observed during the study. Five animals died during the study; two males at 300, two males and one female at 1000. Additionally, one male at 100.

DR. KLAASSEN: Was that due -- how did they give this? What's this?

DR. LIEBLER: Gavage.

DR. KLAASEN: I guess I thought they probably missed gavage.

DR. SNYDER: No, they said it was treatment-related. They didn't say it was -- because there were statistically differences in liver enzymes ALT, AST, and then higher liver weights in the males and females, higher renal weights. So there was some toxicity here. And we didn't have a NOAEL for the males. So the Oleamide does apparently have some toxicity here.

DR. BELSITO: I'm sorry. I'm not --

DR. SNYDER: It's on page 14.

DR. BELSITO: So it was 13 weeks.

DR. SNYDER: Page 14.

DR. BELSITO: Yeah, I'm there. So it says 5 animals died during the study: specifically, 2 males at 300 milligrams and 2 males and 1 female at 1000.

DR. SNYDER: Mm-hmm.

DR. BELSITO: One male in the 100 milligrams was killed on Day 27. The day before death, there were no particular clinical signs. At 1000 milligrams, there was at 100 milligrams and 300, there was no change in blood chemistry parameters. So I don't know where you're getting the liver.

DR. SNYDER: It says there was a statistically higher ALT, AST, and ALP in the males.

DR. BELSITO: Treated with three --

DR. SNYDER: Hundred and 1000. It can serve in a higher --

DR. BELSITO: Right. But 300 and 1000.

DR. SNYDER: Yeah.

DR. BELSITO: But the lack of a NOAEL at 100 is not because of that. The lack of NOAEL at 100 is salvation and spontaneous locomotor activity. That was the only thing they saw in males at 100.

It says there was no other change in organ weight in animals treated with 300, 100, no mortality. No observed effect level is not determined in males. And in females, it was 300. And what happened at 100 milligrams in males was spontaneous locomotor activity and salivation. The liver changes were at 300.

MS. LORETZ: This says higher creatinine level in the urine of males treated with 100.

DR. BELSITO: Okay, creatinine -- wait, I missed that. Where?

MS. AKINSULIE: It's kind of in the middle of the paragraph.

DR. SNYDER: Yeah. So we don't have a NOAEL for the males. And so how does the Oleamide compare to all the other ingredients? Because that's all we have tox data on is the Oleamide, both developmental repro. We don't have any absorption data at all, no TK data.

DR. BELSITO: We have DART studies on the Oleamide.

DR. SNYDER: Only on Oleamide.

DR. BELSITO: Right. Do we think that the others will be different?

DR. SNYDER: That's what I'm asking. That was my question.

DR. LIEBLER: So I mean, I think all of these will be absorbed to some extent. The Oleamide is kind of mid-size in this group. And so I think it's the data for the Oleamide would be reasonably representative of the others in this group. I mean, the smaller ones, like the Lauramide, for example, or I think the coca have shorter chain lengths.

DR. HELDRETH: Twelve to 18, but they're in the middle.

DR. LIEBLER: So they'll be more absorbed than the Oleamide which is 18.

DR. BELSITO: Well, I mean, it's insufficient for sensitization of Cocamide MIPA at one percent, as far as I'm concerned, because we have data suggesting they can sensitize. So I have that insufficiency. So if you want to put in other insufficiencies at 28-day dermal --

DR. SNYDER: Well, I think absorption and 28-day dermal.

DR. LIEBLER: Yeah, because only mid-MIPA is a problematic study.

DR. BELSITO: But for which one?

DR. LIEBLER: For all of them.

DR. BELSITO: For all of them?

DR. LIEBLER: Yeah. You know, you could really -- I would say instead of all --

DR. SNYDER: For the smallest.

DR. LIEBLER: -- do the Cocamide, because it's the ones that are the most -- it includes our spread of different chain lengths and it includes the smallest ones which would be most likely extensively absorbed. And that's a single ingredient that, but it contains multiple chains.

DR. BELSITO: So insufficient for absorption or are we saying 28-day dermal?

DR. SNYDER: Well, I mean, Dan's basically saying they're going to be absorbed. So we might as well just go straight for the 18-day dermal, because we know they're going to be absorbed.

DR. BELSITO: So insufficient for 28-day dermal --

DR. SNYDER: If there's any toxicity, then we've got to have --

DR. BELSITO: -- for Cocamide MIPA and sensitization for Cocamide at one percent.

DR. SNYDER: Yeah.

DR. HELDRETH: I also want to bring to your attention for this, late last week I was sent some additional information.

DR. BELSITO: Yeah, for sensitization.

DR. HELDRETH: Okay.

DR. BELSITO: Irritation and genotoxicity. It came in Wave 3 this morning. It didn't really add much.

DR. HELDRETH: Okay. Just making sure.

MS. AKINSULIE: Actually, I wanted to get your attention to Wave 2 data on Cocamide MIPA. We did get acute tox data.

DR. SNYDER: Yeah, that's just --

MS. AKINSULIE: Not very detailed.

DR. SNYDER: That's a dermal acute tox. It doesn't give us anything for the longer-term studies, unfortunately.

DR. HELDRETH: And then looking in the ECHA dossier for these, they propose using things like Lauramide DEA for read across for these ingredients. We didn't include those data here, because we wanted to get the panel's input to see if that's useful. If that's useful, the panel has a whole report on it.

DR. LIEBLER: It's the diethylamine amide.

DR. HELDRETH: Right. Instead of this monosubstituted amide.

DR. LIEBLER: That actually is not a bad suggestion. Fluoroimide DEA got multiple studies.

DR. HELDRETH: I don't remember exactly what other ones. We'd have to take a look.

DR. BELSITO: So the REACH dossiers were -- it's in Wave 3 from this morning.

DR. HELDRETH: Okay.

DR. BELSITO: On capramide MIPA and caprylamide MIPA that aren't cosmetic ingredients, they have genotox, dermo, irritation, ocular irritation. So I don't know if that's going to help us, though, if that's all they have, because we're asking for sensitization on Cocamide at one percent and we're asking for absorption or DART data.

I mean, you can bring it in, but I'm not sure that it's going to answer the questions.

DR. LIEBLER: Its range is right about C10.

DR. HELDRETH: So then we'll bring it in for consideration in the next report.

DR. BELSITO: I mean, bring it in for as much information as we can get on the capramide, caprylamide, and lauramide.

DR. LIEBLER: Yeah, I think we should.

DR. BELSITO: Lauramide is DEA. Sorry.

DR. LIEBLER: Yeah, Lauramide DEA. So the amine part is just a different structure. It's diethylamine amide so --

DR. BELSITO: Is that a read across for you, Dan?

DR. LIEBLER: Yeah, I think so. I mean, I guess the difference here is that would be a chain with the nitrogen coming out to another carbon with two methyls branching off of it or two -- sorry -- two ethyls off of the nitrogen. And this is a single alkyl chain that's branched with the hydroxyl line.

DR. SNYDER: But there's no 28-day dermal and no sensitization.

DR. BELSITO: Yeah, but I mean, we can look at the data.

DR. LIEBLER: Yeah.

DR. BELSITO: It doesn't look like it's going to offer us what we're asking, but --

DR. SNYDER: Right. It certainly supports if we give it the data that --

DR. LIEBLER: I would say that this would fall into the -- Lauramide DEA would fall into the weight of evidence category rather than the read across.

DR. BELSITO: Okay.

DR. LIEBLER: Our read across rules aren't that developed. It's more still kind of -- how's it look? How do you feel?

DR. BELSITO: So we're going to bring in information from the REACH dossier on Capramide and Caprylamide MIPA and the ECHA dossier on Lauramide DEA.

MS. LORETZ: We've been told there's ECHA dossiers on Cocamide MIPA and Isostearamide MIDA that use MEA compounds for read across. It sounds like there's more data out there anyway.

DR. HELDRETH: Right. And if that's the case, we have CIR reports on the MEAs and DEAs --

DR. LIEBLER: Yeah, I mean, that's --

DR. HELDRETH: -- bringing those over.

DR. LIEBLER: -- a little further afield in terms of weight of evidence. The esters, I mean, the amides are what we want, rather than the amine components. And the thing that gives me pause is that this is a monoalkyl amide. And it's got that branch structure and the hydroxyl substitution. So I would like any read across -- first of all, if there's an ECHA dossier on Alkyl Amide MIPA, then that's ideal.

DR. HELDRETH: Spot on.

DR. BELSITO: Are there? Or are there ECHA dossiers on the other amide DEAs?

MS. LORETZ: I'm not sure.

DR. BELSITO: Okay. We need to just look.

DR. LIEBLER: So there might be more stuff. There might be more.

MS. LORETZ: Find out. Yeah, right. Exactly.

DR. LIEBLER: Yeah. Okay. That's good. So he's to look.

DR. HELDRETH: For the methyl, the one we found is the one Alice is showing. They called it C8 to C10 alkyl MIPA or whatever. But we put it in here in names that are similar to --

DR. LIEBLER: Yeah, that's going to be like cocoa amide.

DR. HELDRETH: Right.

DR. BELSITO: And then in response to the question that in Wave 2, about simply getting a statement about LD50 values without supporting documentation, I think we've used those before; and you said since the lack of detail, does the panel recommend adding these data to the safety assessment? It was a question in Wave 2.

DR. SNYDER: I wrote yes.

DR. BELSITO: I wrote yes too.

MARKS TEAM – April 8, 2019

DR. MARKS: Next ingredient is the alkyl amide MIPA. Is it amide or amide? Either one. Okay.

DR. HILL: You can say amide, amide, amide -- all are proper.

DR. MARKS: Okay. So this is the first review of these. Do I have the chemistry right? They're fatty acids plus monoisopropanolamine? That's the MIPA. There are 14 ingredients. We'll decide in a minute are they -- all 14 okay. And then we had some Wave 2 data for method of manufacture and composition. And then, what I'll refer to as Wave 3 data -- Tom and Ron Hill, did you get a chance to look at this memo from Alice that was on this morning? It was geno-tox dermal irritation, ocular irritation. It looked fine other than it's a borderline ocular irritate. But look at -- the table on the second page, I think summarizes it. Did you see that, Tom, from this morning?

DR. BERGFELD: No, it's not there. It's in paper.

DR. MARKS: Yeah. It's paper. It's from this morning.

DR. HILL: It's from the three that we had the reach links in Wave 2 and didn't have a data --? Okay.

DR. MARKS: It's dated April 8. I'll let you look through that memo and the associated table.

DR. HILL: So this was -- let's three. Two of the three dossiers? Or is it just one of the three? There were three links to new reach dossiers.

MS. AKINSULIE: So this is one of the dossiers.

DR. HILL: One of the three?

MS. AKINSULIE: Yes.

DR. HILL: And you just chose this one?

MS. AKINSULIE: Well, the other two dossiers were on unnamed constituents and not necessarily on the ingredient -- the isotheromide or any of the MIPAs in the report.

DR. HILL: Okay.

DR. EISENMANN: As I understand it, they used MEA to read across.

DR. HILL: Oh, okay. Thank you for not including that.

MS. FIUME: Actually, it was a lauramide DEA that they were proposing for read across.

DR. EISENMANN: Maybe we're looking at -- there's multiple dossiers. I could have been looking at one and one endpoint. But the one I noted was an MEA, but I don't doubt that they were also using something else for it.

DR. HILL: Well, after the cyclohexanol read across for benzyl salicylate, I'm putting less stock in their work by the day.

DR. MARKS: Okay. Ron, Tom, ready?

DR. HILL: Yeah.

DR. MARKS: Okay. So this is a first review of these 14 ingredients. Ron, Tom, are you okay with these ingredients as a grouping?

DR. HILL: Hold on one second. I think so.

DR. SLAGA: I had no concerns.

DR. HILL: I'm sorry. I was looking ahead at concentrations of use, again. I think so. Oh, no. The MIPA-myristate is a salt. That doesn't go there.

DR. MARKS: So myristamide --

DR. HILL: M-I-P-A myristate is a salt. It's just a simple salt between myristic acid and monoisopropanolamine, and I didn't see that there was any use in reading across from that at all. And there was another one I flagged as may not belong, and I need to remember why. Hydroxyethyl stearamide, I'm not sure the structure is correct in the first place. And if it is, I don't know that it belongs in here.

I bet anything that structure is incorrect because I bet it's inhydroxyethyl instead of hydroxyethyl as shown. And I don't know if this is a structure we added or if it's actually in the dictionary that way. I didn't cross-check. I'm sorry. If you go to page 17 -- if you want to look at the structure I'm talking about, it's the third entry in table one.

DR. MARKS: So I think tomorrow, we're going to be at an insufficient data announcement, so these things -- I think, Ron Hill, why don't you go ahead and comment in terms of should these be included. This is the time, obviously, to do that. Let's see what the other team has to say about it and maybe Bart, too. So include two ingredients, question mark, Ron Hill. Okay. Shall I read what -- I think, Tom, you've already seen what Ron Shank's comments are, but I will go ahead and read that.

"Suggest that oleamide MIPA be used for read across except for hydroxyethyl stearamide MIPA and possibly MIPA-myristate." And of course, you were wondering, Ron Hill, whether MIPA-myristate, since it's a salt, should be in this group -- "neither of which is used in cosmetics. MIPA and the fatty acids have already been reviewed by the panel and found to be safe as used. Don't need additional systemic tox if oleamide MIPA can be used for read-across.

Needs: skin sensitization data available for oleamide MIPA. Is it a high concentration and found to be sensitizing? Need HRIPT data and use concentration if read across cannot be used. Then need HRIPT on cocamide MIPA at the one percent highest leave on." I have similar -- although, I said HRIPT for not only cocamide but lauramide and oleamide at leave on use concentration. And as Ron Shank mentioned, oleamide MIPA is a sensitizer at 10 percent, so we need to go down to the use concentration of these ingredients and confirm they're not sensitizers. Other comments? Any other needs, Ron or Tom?

DR. SLAGA: In terms of genotoxicity, we did get some today, and there was some in here. The only thing I had was sensitization data, as you pointed out.

DR. HILL: So is there a reason -- I mean, what we have for chronic tox repeated dose is oleamide MIPA dermal and oral, and that's it. And then we have an oral dart for oleamide MIPA. So my note was is there a reason why we think that we don't need chronic tox on some of these others -- or sub-chronic or something? And that's why I wondered about that other reach dossier is if there was more available information regarding chronic tox because that's not what's picked up in this summary. And it didn't get a chance to go into it and find out.

DR. MARKS: So Ron Hill, are you talking about a 28-day dermal or what?

DR. HILL: That's where I was bouncing ahead to the --

DR. SLAGA: You were talking about systemic, right?

DR. HILL: Systemic, yes. Because the oleamide is a large chain, C18, and it's also unsaturated. But we have substances that could insert into lipid bilayers and accumulate potentially.

DR. MARKS: So Ron Shank it would appear feels that oleamide MIPA -- we don't need it because he wants to use -- don't need additional systemic tox data that if oleamide MIPA can be used for read-across.

DR. HILL: And that's the question because that's what we've got. I mean, they did use 13 weeks at some fairly high doses. And then similarly, for the DART studies, they had a significant number -- all in Sprague Dawley, it looks like. And then they have a reproductive OECD in Sprague Dawley. And the doses were pretty robust.

DR. SLAGA: They were doing that for one, though -- very high doses.

DR. HILL: Huh? Yeah. We have high doses for just that one, so then the question is is that sufficient given the --

DR. SLAGA: For read across. I thought it was.

DR. HILL: And I don't know.

DR. SLAGA: I don't either.

DR. MARKS: Okay, Ron. So I'll issue the comment. I mean, this is going to go out as an insufficient data announcement, so I'll have you comment tomorrow after Don has made the motion for his team. And then we'll see where things land as far as sensitization -- those two ingredients you mentioned -- and systemic tox read across.

DR. HILL: What I also wrote in that regard, though, was that the highest concentration of use in a leave on is at one percent, so that's why I was scrambling to see what about the lauramide. Because if there's going to be dermal penetrability, that sort of chain would be the one.

DR. MARKS: And we don't have a leave on concentration with lauramide, according to my notes. The oleamide is 0.4 percent, and there's a lot of uses with the lauramide.

DR. HILL: Something was at one percent in a leave on and that's where --

DR. MARKS: Yeah. That was cocamide.

DR. HILL: So that has some shorter chains but not predominantly. That's mostly longer chains.

DR. MARKS: We have the leave on for cocamide at one percent and oleamide at 0.4 percent. We have nothing reported for lauramide, and that has 485 uses. That has the highest number of uses.

DR. BERGFELD: There's a dermal contact in there at 4.8 the highest?

DR. HILL: Yeah, and I think that's rinse off because this would be surfeit. And the only doubt I had was hair, non-coloring at two percent for lauramide. And then I was going into the actual raw data table.

DR. MARKS: Oh, dermal. I always look right at the top -- at leave on versus rinse off.

MS. FIUME: It's in a shampoo?

DR. MARKS: Yeah. Here it says not reported, but that's a shampoo. I always want to see the leave on.

DR. HILL: So it also has -- so here's the grey area for me always -- skin cleansing cold creams. So some people leave those suckers on, and, theoretically, they're not.

DR. MARKS: Some I would expect to be left on. Okay. So I think we have discussant points for tomorrow. I think we're going to move forward with an insufficient data announcement. I'd be surprised if it's other than that, and the question is what's going to be the insufficient data that we want. And I think we will arrive at that when we have the cross-discussion between --

DR. HILL: Let me look and see if I had anything else on here. I apologize.

DR. MARKS: Good. No. Good, Ron.

DR. HILL: Now would be the time.

DR. MARKS: Between now and tomorrow because I'm going to ask for you to comment a lot.

DR. HILL: There's some comments I had about the chemistry writing that I think is just writing, such as -- in the dictionary entries, if those are actually the dictionary entries, that say mixture of isopropanolamides, but we only have one pure acid in some cases. So clearly, it would not be a mixture if it's coconut or palm or peanut, but some of them say stearic, oleic, lauric, myristic, linoleic, ricinoleic. Those should be pure, single fatty acids, and then the dictionary still says a mixture of isopropanolamides of -- and I don't think that's accurate.

DR. EISENMANN: I had that same question, and I went to Joanne. And I asked her what does that mixture mean and she wasn't sure. So she discussed it with the committee, and the definitions have not been changed. So they refer to the structure now because I didn't know what that meant -- mixture of isopropanolamides.

DR. HILL: Sometimes it can be that it says steric but it's actually a mixture.

DR. EISENMANN: And she originally said, "Well, maybe it means mono-died."

DR. HILL: That's not possible.

DR. EISENMANN: And then she said, "No, that's not." So if you look in the dictionary now, the definitions have been changed to refer to the structure.

DR. HILL: Okay. Great. That helps that one.

DR. EISENMANN: Because I had that same question. I didn't know what that meant.

DR. HILL: Okay. Great. That was actually one of the biggest gaps. And let's see. I think we do want to look at that REACH data, and I apologize. I didn't get a chance to see if there's any chronic tox in there because that could be really helpful because we have shorter chains. I think that's a C10 and C8. So if we had data from that, we would have read across, and it would be beautiful.

MS. AKINSULIE: So for the other dossiers, they were either read across for lauramide DEA or an unnamed constituent, which we're not sure if it's actually on that ingredient specifically.

DR. HILL: You said on what?

MS. AKINSULIE: On either lauramide DEA or unnamed constituent.

DR. HILL: So what I'm looking at is the capromyid and the acrylamide?

MS. AKINSULIE: Yes, which is a proposed read across on the dossier.

DR. HILL: Okay. Well, that makes sense because it's monoisopropanol. It's not a cosmetic ingredient, but if those -- if we have good chronic tox data on that, we definitely need to roll that in because that would definitely help us.

MS. AKINSULIE: So what's on the table is all the information --

DR. HILL: -- it's all they have? It's the geno-tox, the epidermal --

MS. AKINSULIE: -- irritation.

DR. HILL: Okay. That's unfortunate. All right.

MS. FIUME: So Dr. Hill, in those dossiers, to support the information, they will pool a number of other substances, which is why -- as part of the question -- and I think it was answered -- is what we saw was the lauramide DEA being used as read across. I believe Carol said she saw an MEA. And if the panel agreed with that information to support it because then we would pull in our own report. Okay. So that's why it wasn't included here because we didn't know if you would accept -- would want something like lauramide DEA for read across information.

DR. HILL: I don't think it should be because that's a diethanolamine. And that's why I was wondering, actually, about that one stray structure because I think that one that says hydroxyethyl -- I suspect that may not be the right structure. But either way, it doesn't fit with the rest of them. Okay. Just a general comment about using the language "structurally similar," but I wrote it in the document just so that -- because I, again, want to just please, please, please remember that similar only means -- has meaning with relation to a particular safety endpoint. Otherwise, we could talk about something like a Tanimoto similarity index. But otherwise, similar is meaningless. We can say analogous, but if it's an analog, it's an analog for what biology or what biological endpoint that we're talking about? So I put those comments in there. You can feel free to pass them along to your administrators so they can get the same soapbox speech. But to say something is structurally similar, what biological endpoint are we talking about or what safety assessment endpoint?

DR. MARKS: Okay. Any other comments?

DR. HILL: They only thing I did want to point out in this -- again, I think a language and writing thing -- is that the safety of the component fatty acids, as well as isopropanolamine are of importance, with respect to their presence as impurities. But unless we have ADME data that suggests that those amides are actually cleaved in the skin, then the pertinence is probably nil. That's it.

DR. MARKS: Okay. Ready to move on to the next ingredient?

MS. FIUME: Dr. Marks? I do have a question on some of the Wave 2 data that were received. It'd be on page six of the Wave 2 submission. Again, it's whether or not the panel would want this information reflected in the report. The source is anonymous, and for acute toxicity, it's on the cocamide MIPA. It simply has dermal LD50, rabbit greater than 2000 milligrams per kilogram, or oral LD50 rat greater than 2000 milligrams per kilogram.

DR. HILL: So I presume those are acute studies, right?

MS. FIUME: It's an acute study. There are no details as to whether there were other doses or how many animals and what the patches may have been for the oral. We're assuming gavage. Is that information that the panel finds acceptable for inclusion in the report?

DR. HILL: If it's oral, it's bound to be gavage, but dermals is different because surface area matters massively for dermal.

DR. EISENMANN: But it's probably a standard limit test, or they're just giving them the 2,000 milligram and they didn't see anything -- done for transportation purposes.

DR. HILL: Yeah. I gotcha.

DR. EISENMANN: I would include -- my advice is to include it but say that's all you've got so the reader knows that you don't have more details. I think that's all you can do.

MS. FIUME: I guess our concern was was it almost appears as if it could have been pulled from an MSDS. And normally, it's been our practice that we don't include MSDS information in the reports. So we didn't know -- the source was anonymous, so we didn't know if it was done by someone who actually did the studies, if it was pulled from an MSDS. We were more concerned about just the total lack of detail in the data submission.

DR. EISENMANN: Didn't it come with some information about the material, though? It came in from industry.

MS. FIUME: There's composition and physical and chemical properties. Again, physical and chemical properties can come from and MSDS or from a supplier. The source was anonymous.

DR. EISENMANN: It came from a supplier. I can tell you that. They don't want their name on your website, so if it's coming anonymously, that's why. They don't want their name on your website.

MS. FIUME: We were more concerned about the lack of details in the study and including information in the reports that don't have any details. I know it's only an acute study, but in the other case, it was irritation and sensitization. So it seems we're getting more submissions that have zero details. So I guess I'm asking for the panel's input, overall, on their acceptability of data that's being submitted as unpublished data with zero details.

DR. HILL: So if there's an oral LD50, and it says oral LD50 on an MSDS, to me, that's a very reliable source of information. If it's a dose that's fairly large, it's got to be gavage because otherwise you're trying to feed something to the animal that they're not going to eat unless it's really sweet or something -- like sorbitol. For me -- and a manufacturer, if they put that on their material safety data sheet and they can't back it up with data, the liability would just be incredibly huge. I can't imagine them even doing that. So if you reference it as an MSDS specifically, source unidentified, I realize that might create some issue. But for me, it's a data point. Now, sensitization, that's different because, unless you know the details of how it was performed, you don't know what you're getting. But for me -- and I don't know. Dermal LD50, can we rely that it's -- if they have an OECD procedure, then you know what they did. If they don't…

MS. FIUME: There's no number of animals. It's just saying it was in rabbit and giving a dose. So I guess our concern is the information --

DR. EISENMANN: It may be just one animal. It's a limit test. They just put the maximum amount on the animal, and if it doesn't die, they might not do anything more.

MS. FIUME: But my concern is we don't know any of those details.

DR. EISENMANN: Correct, and you can say you don't know any details and that a dermal LD50 was -- that happens in published papers, too, where you only get an LD50 value stated.

DR. HILL: You could consider, if it's not in the main report, putting it in a table -- a summary table, if there is such a table. If it's only one data point, you wouldn't make a table.

MS. FIUME: It was more of just raising concern that more and more often we're receiving data that do not have any details. So I just didn't know if the panel had the same concern that we were seeing as we're capturing the information in the documents.

DR. HILL: I certainly do. If it's a data point but there's not detail, it's not a data point, right?

MR. GERMILLION: Are anonymous sources of data -- is that something that has been going on throughout the history, or is that relatively recent?

MS. FIUME: No, it is acceptable because on -- when we put out our announcements or we send out our reports, we ask for data. And we do say that, if you don't want your name disclosed, you can send us the information. So it's not as much concern that it's an anonymous source. It was the lack of details. Because as Carol said, sometimes the company doesn't want their name -- because it does go on the website when the books are -- when our panel material is posted on the website and in our reports.

MR. GERMILLION: But the trend you're highlighting then doesn't have anything to do with anonymity? Okay.

DR. MARKS: Monice, did you get the answer for that? My sense is that as long as you document the amount of data you have, as Carol suggested, unless the panel members say -- sometimes we say the study isn't valid or this paper isn't valid. Delete it. I think as long as you say the parameters, if it helps decide on the toxicity, then it should be included. And we acknowledge we may not know all the details. But just as the earlier discussion, when an HRIPT was done, I will assume that when they use that terminology, they're having repeated challenges with the ingredient. And the results will determine whether that testing was a cause of sensitization or not. So I don't need any more details. It's an HRIPT. I'm going to assume they did it in a standardized method.

DR. HILL: And I will say this. In working in the lab or supervising students working in labs, I relied very heavily on MSDS, as we have, to be able to keep them on file or make sure that whoever was working -- if they're working with any chemical -- had access to those. There's some sense of reliability there that, if a piece of information about safety and hazard is on there, that company would be able to back it because -- and I don't know what the up to the date code of federal regulations are or policy memos in OSHA or for transport purposes EPA -- but I think mainly in terms of OSHA and occupational safety. If there's a piece of information on MSDS, it had better be valid. It could, I guess, be one rat, hypothetically. But in most cases -- and especially if it's a lower limit -- I suspect they would have done more work, and that limit could be backed.

MS. KOWCZ: I just have to confirm what Ron is saying. Usually when you're in the lab developing anything or you're in production plans -- you're handling your transportation, whatever -- always have the MSDSs. I don't know what the federal regulations are, but for us, in different industries and in the industry we're working in right now, it was a requirement. It came with the material. If it didn't come with the material, we never used the material. We'd have to go back to the suppliers. So you had a very good sense of confirmation that the testing was done and that it was proper because you aren't exposing people to work with this material, whether in a large scale or a small scale. So I have to agree with Ron on this.

DR. HILL: And part of the reason that I didn't feel fully confident is because some of those regs have been changing recently a good bit. And even the form of the MSDS has changed. So I'm not up to date with the letter of the law because I'm, right now, not riding hard on students where I have to worry about that.

DR. MARKS: Point of clarification for me. Has the terminology also been changed from --

MS. KOWCZ: Yes.

DR. MARKS: It used to be MSDS.

MS. KOWCZ: It's SDS, Safety Data Sheet.

DR. MARKS: Safety Data Sheets, yeah. Okay. So it's SDS is the more current terminology. Okay. Good. Any other comments? Okay. If not, Ron Hill, I'll be asking you to clarify -- or to discuss the two ingredients which you have questions whether they should be included in the systemic tox read across. And then I'll be mentioning the sensitization needs. I think that's pretty straightforward. The question is do you need the three that I mentioned, or can you use oleamide and read across? I'd like to see all three, quite frankly. But okay. Let me go ahead and close this.

FULL PANEL – April 9, 2019

DR. BELSITO: So this is the first time we're looking at this group of materials. We thought that it was insufficient. We needed a 28-day dermal for cocamide MIPA; and if positive, additional data. We wanted to bring in the REACH dossier on capramide and caprylamide MIPA, and the ECHA dossier on lauramide DEA and possibly other similar materials.

We wanted sensitization data for cocamide MIPA at 1 percent, and, obviously, in the discussion, restrictions of nitrosation and residual nitrosamines in the discussion.

DR. BERGFELD: Is there a second?

DR. MARKS: Yes, we second that. So discussion points, we also felt we'd like to see, since oleamide MIPA is a sensitizer, we'd like to see the HRIPT or sensitization of what level would be safe. And then also, you had asked for cocamide, did you want lauramide, or did you think you could read across for sensitivity?

DR. BELSITO: Cocamide was one in highest leave-on at 1 percent, so we asked for cocamide at 1 percent.

DR. MARKS: Yeah, that's fine. And then, Ron Hill, do you want to comment? There are two ingredients, which you were concerned about systemic toxicity and read across, but maybe that's already been addressed? Yeah.

DR. HILL: It is? Okay. Because I think the identity of the two ingredients that should be removed here, should not stay in. Actually one of them, I'm not clear because we don't know for sure what it is.

DR. MARKS: So that was the hydroxyethyl stearamide MIPA.

DR. HILL: Hydroxyethyl -- yeah, which I think that structure is probably wrong, and it needs to be researched. But either way --

DR. MARKS: Yeah, and then the MIPA-myristate.

DR. HILL: Yes, the one that's just a salt, the myristate, it's just a salt. It's not an amide, so disparate.

DR. BERGFELD: Any other comments?

DR. HILL: And actually, there would be no safety issues with that one, because we've already evaluated and assessed myristic acid. We've already evaluated and assessed the amine cation here, and both of those have been cleared. So there's no reason to have that in here, it doesn't belong in the salts.

The other one, I think it's probably N-hydroxyethyl, as opposed to the structure that's given, I wasn't sure if that structure was added by staff, or if that's the one that's in the dictionary. But even if it's in the dictionary that way, it may not be right. So like our souped-up aspirin that we dropped, because we found out we had the wrong structure.

DR. BERGFELD: Okay, so we have a motion to send out an IDA, which is an insufficient data announcement, with the needs. And do you have the needs?

MS. AKINSULIE: Yes.

DR. BERGFELD: Okay.

MS. AKINSULIE: I do have a question.

DR. BERGFELD: Please.

MS. AKINSULIE: So I wanted to get clarification to see if the panel wanted to add the data on lauramide DEA for read across or for weight of evidence?

DR. LIEBLER: Weight of evidence.

MS. AKINSULIE: Yes.

DR. BERGFELD: So it looks like consensus to add the DEA. Well, I call for the question then. All those in favor of sending out an IDA on this --

DR. HILL: What is -- wait a minute. What is lauramide DEA? I'm trying to remember structure.

DR. LIEBLER: Diethanolamine amide.

DR. HILL: Yeah, that's what I thought.

DR. LIEBLER: So it's not strictly analogous structure, but it is a fatty acyl amide. It's a dialkyl substance. So weight of evidence, as opposed to read across. I didn't think the read across was quite good. But the weight of evidence could be helpful. We'll have the data to consider as we move forward.

DR. HILL: Yeah, that's fine. That's fine. I just wanted to make sure I was clear on what we were doing.

DR. LIEBLER: Yep.

DR. HILL: So, sorry for that.

DR. BERGFELD: Any other questions before I call the question?

DR. HILL: I wonder if we could at least add something about dermal ADME information. I mean, it's 1 percent, but again, we have a synthetic lipid. I don't know anything about what might or might not happen to that in skin.

Otherwise, it's going to insert in membranes, and we don't know what goes on there. So, if we could get some information about what's known about what happens to this stuff in skin, specifically. No concerns systemically at all. In fact, I don't even know that we need the dermal tox, but it's from their group, so --

DR. MARKS: Could I ask Dan, what did you think about the two ingredients which Ron had concerned about, including in this report, the hydroxyethylstearamide MIPA, and the MIPA myristate?

DR. LIEBLER: So I thought the MIPA myristate is a coin flip, frankly. Yes, it is a salt rather than the amide; but essentially, it has similar use, it has the same components. I lean towards keeping it in, but I'm not going to battle over that. With the other one, the hydroxyethylstearamide MIPA, I think there is a legitimate question as to what the structure, what the identity of it is.

DR. HELDRETH: So this is the structure that's in the dictionary, whether that's correct or not.

DR. LIEBLER: That's the structure in the dictionary; then we review it.

DR. HILL: Okay, just don't expect me to read across.

DR. MARKS: Thank you.

DR. BERGFELD: All right, are we ready to call the question?

DR. HELDRETH: I do have two more questions.

DR. BERGFELD: Okay.

DR. HELDRETH: So for the information that we will bring in for weight of evidence, specifically for lauramide DEA. My first question is how do you want that presented in the report? Do you want that as, say, an appendix or some trailing set of information?

And the second question is, the panel has done previously a report on alkyl amide DEA's. So there's a body of toxicity data relating to those ingredients. Is that also something that you would like to see as part of this report, or just the data we're seeing from ECHA dossier?

DR. BERGFELD: Dan? Ron Hill?

DR. HILL: I don't think it should be in there because I don't think it -- I mean, I don't know, maybe it adds to the weight of evidence, but for me, it does not. The nature of the amide, what the amide is made with, is disparate; so yes, we could N diethylate. We could di-diethylate and end up with just a primary amide there. But I don't think that that necessarily corresponds at all to the isopropyl, the hydroxy head group in terms of how this would be bio handled. So, for me, it doesn't really add to my weight of evidence and --

DR. BERGFELD: Dan?

DR. LIEBLER: So I agree. We don't need it.

DR. BERGFELD: Okay. Can we call the question now? All those in favor, then, indicate by raising your hand. Thank you. Unanimous. So we're moving ahead with an insufficient data announcement.

SEPTEMBER 2019 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

BELSITO TEAM – September 16, 2019

DR. BELSITO: Okay. MIPA. We have that little map on the ECHA dossier, which really raises concerns when they say it's Isostearamide, but it was really cocamide; and it was cocamide, but it was really Isostearamide. Do they know what they're talking about?

MS. FIUME: I will explain what happened. And if you'd like, I have copies of the report that has the same information. But I have what we said the test article was and have what the actual test article is. So, you're welcome to look at it or not, but I will distribute it.

DR. BELSITO: No, I believe your summary.

DR. KLAASSEN: Yeah, as long as it's correct.

MS. FIUME: Well, and I didn't know if it helped to decide if read-across was applicable, if you actually saw where they fell in the report. So, if you don't want it, feel free to not look at it.

So those dossiers were a little different than we've dealt with before. Where for the test article it named, say, cocamide MIPA as the test article. And then it wasn't until you got into the executive summary where they mention something else that was actually tested.

So, we didn't figure that out, unfortunately, until after we received the first version. So I apologize. But I haven't seen them do that before, so it was very confusing to figure out what was actually tested in each of those studies. But I think we have it figured out now.

DR. BELSITO: So we have a 14-week dermal that had skin effects like proliferation, increased sebaceous glands, but no end organ effect. We had clean GPM -- guinea pig maximization -- test for cocamide and Isostearamide. For oleamide, we have induction at 10 percent intradermal, followed by a 75 percent topical induction and a challenge at 50 percent, which is extraordinarily high, that gave positive results. Otherwise, at concentrations of use everything was negative.

I think we restrict for nitrosamine formation. We talk about peanut oil. EU limits the amount of protein in peanut oil, we've never done that. I don't know how we handled the peanut ingredient. And I'm not even sure we need to say formulated to be non-irritating at the concentrations that they're using here.

But if we wanted to be safe, we'd say safe as used when formulated to be non-irritating. And in the discussion talk about nitrosamine formation and peanut proteins in peanut oil and be done with it. That's what I read. And I had little comments along the way, but to sum it up since it's 4:00. Paul, Curt, Dan?

DR. LIEBLER: I didn't catch all of what was with this. I know that there was the ambiguity about the thing with Isostearamide.

MS. FIUME: This version, what it shows is what it originally said was being reviewed, and that's crossed out. And then it indicates what ECHA used as proposed to read across.

So, a lot of this information is -- so I tried to gray out where they are, the read-across, to see, is the read-across acceptable? Or do you want it in the report or not want it in the report? But it was just to help with that little table that you were given in Wave 2.

DR. LIEBLER: Okay. N,N-bis(hydroxyethyl).

MS. FIUME: Bart said he believes that these ingredients are actually diethanolamides.

DR. LIEBLER: Yeah. Right. I had notes to myself. Like the lauramide DEA, for example, up to 10 percent was relevant. I remember when I was looking at this. If this were RIFM, we would have no problem agreeing to these as read-across for the sensitizations done. The DEA, the diethanolamides for these MIPAs. And what you have here in this new information is the N,N-bis(hydroxyethyl).

DR. BELSITO: Yeah, but at huge concentrations. This is a guinea pig maximization test where they intradermally gave 10 percent, followed by a topical challenge with 75 -- or topical induction.

So, guinea pig they do intradermal with Freund's Complete Adjuvant. Then they slap an occlusive patch on 8 days later. And then 35 days later they come back with the topical application.

So the intradermal was 10; the inclusion for sensitization was 75; and they challenged with 50 percent.

DR. SNYDER: Okay.

DR. BELSITO: I mean, it's --

DR. SNYDER: Ridiculous.

DR. BELSITO: It's ridiculous. So, it's a sensitizer, but there's no data to suggest that at concentrations where these are used they're sensitizing.

DR. LIEBLER: Right. So, you don't feel we need to bring in any read across sensitization safety data?

DR. BELSITO: No.

DR. LIEBLER: Okay. Well, if we did, I'd be fine with it.

MS. FIUME: What about the other read across? Under carcinogenicity and under the DART section and the tox section?

DR. LIEBLER: Yes. All okay.

MS. FIUME: Okay. Then my next question is, so this was ECHA's read-across. We have a report of diethanolamides that the CIR has done itself. Do you want any of that information?

DR. LIEBLER: Yes.

MS. FIUME: Any specific diethanolamides? Cocamide, lauramide?

DR. LIEBLER: Lauramide, DEA and -- so let's see. You had -- you must've had -- for which endpoint?

MS. FIUME: Yes. Under the tox.

DR. LIEBLER: Under the tox?

MS. FIUME: Because originally dermal tox was asked for in the original --

DR. LIEBLER: Okay. Before hearing Don's comments, I thought we also needed data for sensitization. So, Don feels like we don't, so fine. But from the other report with the Lauramide DEA, up to 10 percent is relevant. Lauramide and cocamide DEA would be relevant to these MIPAs.

MS. FIUME: Okay. So, bring that in from the old report where there were data entry points that were missing?

DR. LIEBLER: If you can do that. Correct.

MS. FIUME: So, would the oleamide DEA also be relevant to bring in?

DR. LIEBLER: Sure, for linoleamide MIPA. Let's see.

DR. SNYDER: We already have good data on it though.

DR. LIEBLER: Any equivalent "blank" and unsaturation of fatty acid version of DEA or dihydroxy, bis(hydroxyethyl) -- any of those are okay because they're very similar to the MIPA. They all have equivalent featured structure alerts. None of them have -- including our ingredients -- any carcinogenesis structure alerts; or any other specific toxicity-related structure alerts, including sensitization, for that matter.

DR. SNYDER: Okay. Chop chop.

DR. BELSITO: So, safe when formulated to be non-irritating. Or do we even need irritation? And if we want to cover our butts, there are some irritation data. I think they're high, but we know that's always formulation. So, it's easy enough just to add.

DR. SNYDER: So, we're going to cover our butts to minimize irritation, is that what you're saying?

DR. BELSITO: Um-hm. Yeah.

DR. SNYDER: Okay.

DR. BELSITO: Okay? Anything else?

DR. SNYDER: I think we've got it.

DR. BELSITO: Okay.

MARKS TEAM – September 16, 2019

DR. MARKS: I don't think there was anything of concern. Okay. So this is a draft safety assessment of alkyl amide MIPA ingredients. In April of this year, an insufficient data announcement was issued needing sensitization data for cocamide MIPA; skin sensitization on the other alkyl amide MIPAs; and a 28 day dermal tox on cocamide MIPA, if positive additional data. And let me see. We got data before the April meeting in Wave 2.

Ron and Tom, your comments? We didn't get any -- we did get a Wave 2. The highest concentration for oleamide MIPA is now 0.4 percent. And then we got an ECHA, E-C-H-A, data is being provided.

And then, in a previous meeting, Ron, you had raised the issue of really do we need systemic toxicity for all these ingredients, or could we just read across from the oleamide. And then we have this ECHA. We're at a position to issue a tentative report. Can we move forward? Ron, Tom, your comments?

DR. SHANK: All of the adverse responses were at concentrations well above cosmetic formulations. The DART studies were negative. The genotox was negative, except for isostearamide, which was clastogenic. But it was clastogenic at cytotoxic levels, so that is not important.

The mouse carcinogenicity study was positive, but this is a common thing. The mouse has -- the untreated mouse, controlled mice, have an incidence of liver cancer and kidney cancer. And that was increased in the carcinogenicity study. But this was at concentrations that were irritating. So you go to the rat carcinogenicity study, which was negative.

So I don't think there's a genotoxicity or carcinogenicity problem. Skin sensitization was positive, but only at very high concentrations well above cosmetic use levels. So I'd say it's safe for rinse offs. And the maximum leave on concentrations for cocamide and oleamide are 0.4 percent, well below any toxicological concern. We don't have a concentration of use for isostearamide that I could find, so it seems to me safe as used.

DR. MARKS: Yeah. My comment was do we still need the sensitization data for the 0.4 percent use concentration, oleamide MIPA use concentration? We know it was a sensitizer at 10 percent, but we don't know at what level it's not a sensitizer. So I kind of kept that as an insufficient data need and safe for the other 13.

DR. SHANK: Okay.

DR. MARKS: Now, page 29. Let's go there a second because sensitization for cocamide MIPA, five percent, the guinea pig maximization. So on Page 29, if you look at the first paragraph under animal cocamide MIPA, it says the sensitization potential of cocamide MIPA. And then if you go down to the next sentence, it says two injections of five percent isostearamide MIPA. So I'm wondering is this really cocamide MIPA they were using?

MS. FIUME: Sorry. That was a typo. It was cocamide MIPA.

DR. MARKS: Okay. Good. I wanted to clarify that to be sure. So my feeling then, as I said before. So we'll just clarify that typo. So that is okay.

So Tom, your comments? I think for me it's still, do you feel comfortable saying that even though it's relatively low concentration, 0.4 percent -- but parts per million it isn't -- the oleamide MIPA use concentration, I still want to see some sort of sensitization data since we have a sensitization alert in there. And that's the only one I would put as insufficient.

DR. SLAGA: I agree.

DR. SHANK: But not the cocamide?

DR. MARKS: No. The cocamide MIPA, the five percent guinea pig max was okay, so I think that's fine. The highest use concentration I had was one percent with it, so we're well above that.

DR. SHANK: Okay.

DR. MARKS: And I just wanted to clarify the typo in there and be sure which ingredient was really being used.

DR. BERGFELD: I'm sorry. Which one do you want your sensitization testing on?

DR. MARKS: That would be the oleamide MIPA.

MS. FIUME: So Jim, can I ask, now that you've discussed some of it, this was the report that there was all the confusion with the ECHA. So a lot of the information -- the way it was presented originally -- the way this presented in the ECHA dossier, it's test substance. And it would be cocamide MIPA or something equivalent. And then when you got down to the executive summary, they stated what was actually tested. So that's where my confusion came in.

So in the Wave 2, I provided the table showing what was actually tested each time. And sometimes it was the ingredient and sometimes it was a read across ingredient. Did that make sense to what I changed, and is the read across information acceptable?

I don't know if you've had a chance to really look and see what it changed because the DART studies were actually on a read-across ingredient, which I believe was a DEA ingredient, either cocamide or lauramide. The genotox was correct as provided. The carcinogenicity study was actually on a read-across ingredient. The four hour inclusive dermal irritation was on a read-across ingredient.

So I just need to know if -- and I apologize that it was so confusing. It took us a while to really figure out what ECHA had done and what their studies were on.

DR. SHANK: The table in your hand, is that in the report?

MS. FIUME: This was in Wave 2. A lot of this was the tox data. I will hand this to you.

DR. SHANK: Why didn't I see this?

MS. FIUME: You wouldn't of received a new report, but you would have gotten the table that we coded what was what.

DR. SHANK: In Wave 2, what page is that on, please?

MS. FIUME: Let me find it. It would have been page 3.

DR. SHANK: The read-across seemed to be probably okay for the genotox and carcinogenicity or, I guess, just the carcinogenicity. I'd like confirmation from Dr. Liebler on that, but it seems to me a reasonable read-across. So that doesn't change -- I still think these are safe for rinse offs, and I go along with Dr. Marks' skin sensitization for oleamide MIPA at use concentration of 0.4 percent.

DR. SLAGA: We need the 28 dermal, right, because of the --?

DR. SHANK: I don't think we need the 28 dermal.

DR. SLAGA: That's what I initially thought.

DR. MARKS: So Tom, you're okay, then, moving tentative report safe for 13, insufficient for the oleamide MIPA in the sensitization data for use concentration? Okay. Good. Monice, here. I'll give you this back. Thank you.

FULL PANEL – September 17, 2019

DR. MARKS: So at the April 2019 panel meeting we issued an insufficient data announcement requesting skin sensitization data for cocamide MIPA along with the alkyl amide MIPAs, and a 28-day dermal tox on cocamide MIPA. And, we did receive some data.

Our team moves that a tentative report be issued safe for 13 of the ingredients, and an insufficient only for the lauramide MIPA since we don't have sensitization data on the leave-on concentration at 0.4 percent. And there was an alert that this ingredient could cause sensitization at 10 percent. We do not know what level is at which it would not cause sensitization. We did a lot of reading across on this, which if need be Ron could illuminate.

DR. BERGFELD: Is there a second, or a comment?

DR. BELSITO: Yeah, the isostearamide, or the oleamide, which you're going insufficient for sensitization.

DR. MARKS: Correct.

DR. BELSITO: We thought we could read across from the cocamide and Isostearamide; particularly in light of the fact that, again, with the oleamide, there was a guinea pig maximization test where they were given 10 percent intradermally and then sensitized topically with 75 percent and challenged with 50 percent, which is significantly higher than the 0.4 percent of which it's being used.

And when you look at the data for all of these other amides MIPAs, they're pretty clean at those low concentrations. So we felt that, yeah, we acknowledge that data, you know, you stress the system if you bring many of the ingredients that we're looking at to high enough concentration you'll induce sensitization. But at the levels used there's no indication that that would occur based upon the read across from the others.

DR. MARKS: So you would move that's safe for 14?

DR. BELSITO: For all of them, yes.

DR. MARKS: For all of them.

DR. BELSITO: And put in the discussion that, you know, what the concentration of use is of the oleamide. And that, yes, there were data showing sensitization in a guinea pig maximization test, but this was at extremely high concentrations.

DR. MARKS: Don, I like your reasoning and so I'll change the motion to safe for all.

DR. BERGFELD: Is there a second?

DR. BELSITO: Seconded.

DR. BERGFELD: Any further --

DR. SHANK: You don't have a use concentration.

DR. BELSITO: Oh, yeah, well, that's part of the discussion, nitrosation.

DR. SNYDER: And non-irritating.

DR. BELSITO: Non-irritating, right.

DR. BERGFELD: So what is the motion then?

DR. BELSITO: Safe as used when formulated to be non-irritating. And in the discussion, not to be formulated with other materials where nitrosation could occur.

DR. SNYDER: Or any other DEAs populated in this report.

DR. BELSITO: Right.

DR. BERGFELD: Now, Ron Shank had a question.

DR. SHANK: We don't have a use concentration for isostearamide. It's not reported, right?

DR. BELSITO: But we assumed that it will be used in concentrations similar to the others. And it's not the isostearamide that's in question, it's the oleamide. And, we have a maximum concentration of 0.5 percent in a rinse-off.

DR. SHANK: But you have no use concentration for the isostearamide.

DR. BELSITO: It wasn't the isostearamide that caused the positive reaction in the guinea pig maximization test, it was the oleamide.

DR. SHANK: Well, it was positive.

DR. BELSITO: What? The positive guinea pig maximization test was on the oleamide, not the isostearamide. Isostearamide and the cocamide were clear. And we have a concentration of 0.5 percent in rinse-offs for the oleamide.

DR. MARKS: And .4 in the leave-ons.

DR. BELSITO: Maybe I'm looking at the whole thing --

DR. MARKS: No, that's fine. It doesn't change the conclusion.

DR. LIEBLER: Ron Shank is correct; I mean we don't have a use concentration reported for the isostearamide. It's not -- in relation to the oleamide we just don't have it. You know, this is a low number of uses ingredient. It's not surprising that sometimes we get no reported use concentrations on those.

I think if we made the assumption that the use range for the type of use, concentration would probably be similar. And, the supporting data indicate that there's really no risk of sensitization. That one assay, I think, Don has explained, and I think Jim has agreed to Don's reasoning on that.

DR. MARKS: Yes.

DR. LIEBLER: So, I think there are a number of other examples where we've had low-use ingredients, particularly in much larger families where we've not had a use concentration. And we've made that assumption bringing that in. So that's what I was assuming here.

DR. BELSITO: We have a negative guinea pig maximization test on the isostearamide. The material in question with the positive guinea pig maximization test, with the intradermal at 10 and topical at 75 is the oleamide -- and it's used at .4 percent in leave-ons.

So, that guinea pig maximization test was exorbitant compared to what is actually used in cosmetic products. And that's why I felt we could go safe as used when formulated to be non-irritating.

DR. BERGFELD: Do you think this can be handled in the discussion?

DR. BELSITO: Yes.

DR. BERGFELD: The lack of concentration, and the explanation you all have given.

DR. BELSITO: This is the isostearamide for which we have safety data.

DR. BERGFELD: I know. That's what I meant.

DR. BELSITO: We always say that we're assuming the materials that have no reported concentration of use, or no reported use, would be used similarly to the other in this report.

DR. BERGFELD: But where are you putting that?

DR. MARKS: That always goes in the conclusion as an asterisk, as I recalled.

So, does that answer Ron? I didn't know why you brought it -- okay.

DR. SHANK: It's not a big thing; but if we say safe as used and we don't have a use concentration, even though we have data at a high level, it should be in the discussion or --

DR. BELSITO: We have data on the isostearamide and it's negative. The data that we're discussing in the guinea pig maximization test is on a totally separate material; it's on the oleamide, for which we do have data on concentration of use.

DR. SHANK: I understand it. It's just when you say safe as used at the concentration and you don't have a concentration.

DR. BELSITO: We do this all the time. We don't have the concentration on many of them --

DR. SHANK: Well we handle that in the discussion, right? We assume --

DR. BELSITO: There's an asterisk someplace that says that materials that aren't reported to be used, or for which we have no concentration, if they were to be used would be used similarly to the other materials reviewed.

DR. SHANK: Fine.

DR. BELSITO: I'm not sure where that occurs; it's a discussion asterisk to the conclusion.

DR. HELDRETH: It follows the conclusion. All of the ingredients that are listed in the conclusion have an asterisk next to them if they're not reported.

DR. BELSITO: Right.

DR. BERGFELD: So obviously this will have an asterisk.

DR. SHANK: Yeah, I want to check the box.

DR. BERGFELD: Okay. Any other discussion regarding this ingredient? Seeing none, call the question, all those in favor indicate by raising your hand. Ron, are you voting or not? Okay, unanimous, thank you.

So, it looks like we're going on to Isopropyl Lanolate, Dr. Belsito.

Safety Assessment of Alkyl Amide MIPA Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: November 15, 2019
Panel Meeting Date: December 9-10, 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.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.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, former CIR Scientific Analyst/Writer, and Monice Fiume, Senior Director.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢
cirinfo@cir-safety.org

ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 14 alkyl amide MIPA ingredients as used in cosmetics. All of these ingredients are reported to function in cosmetics as a surfactant - foam booster and/or viscosity increasing agent. The Panel considered the available data, as well as data on read-across substances, and concluded these ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

INTRODUCTION

The safety of the following 14 alkyl amide MIPA ingredients as used in cosmetics is reviewed in this safety assessment:

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

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all of these ingredients are reported to function in cosmetics as a surfactant – foam booster and/or viscosity increasing agent; some of the ingredients have other reported functions (Table 1).[1] (According to the *Dictionary*, MIPA is a technical name for isopropanolamine.)

The rationale for this grouping of alkyl amide MIPA ingredients stems from the fact that each of the ingredients is a mixture of isopropanolamides of a simple carboxylic acid. These ingredients are classic surfactants and viscosity increasing agents.

Diisopropanolamine, triisopropanolamine, and isopropanolamine are mixed aliphatic amines of isopropyl alcohol. In 1987, CIR published a safety assessment of these ingredients, with the conclusion that diisopropanolamine, triisopropanolamine, and isopropanolamine are safe as cosmetic ingredients in the present practices of use and concentration [as described in that report]; the Panel also concluded that those ingredients should not be used in products containing *N*-nitrosating agents.[2] The Panel later reaffirmed that conclusion.[3] The safety of several components of the alkyl amide MIPA ingredients has also been reviewed.[2-15] The conclusions of these reviews are provided in Table 2.

The Panel also has reviewed the safety of another group of ingredients that are structurally similar to the alkyl amide MIPA ingredients. In 2013, the CIR published a safety assessment of diethanolamides as used in cosmetics; the Panel concluded that diethanolamides are safe in the present practices of use and concentration [as described in that safety assessment] when formulated to be non-irritating, and when the levels of free diethanolamine (DEA) in the diethanolamides do not exceed the present practices of use and concentration of DEA itself.[16] The Expert Panel cautioned that 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 in this report was obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) as part of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) chemical registration process.[17-19] When appropriate, information from these summary documents has been included in this report and is cited to ECHA. It should be noted that some of the information pertains to similar compounds, and has been included for read-across to address gaps in information on the alkyl amide MIPA ingredients.

CHEMISTRY

Definition and Structure

The ingredients reviewed in this report are the fatty amides resulting from the amidation of fatty acids with MIPA.

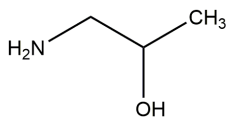


Figure 1. MIPA

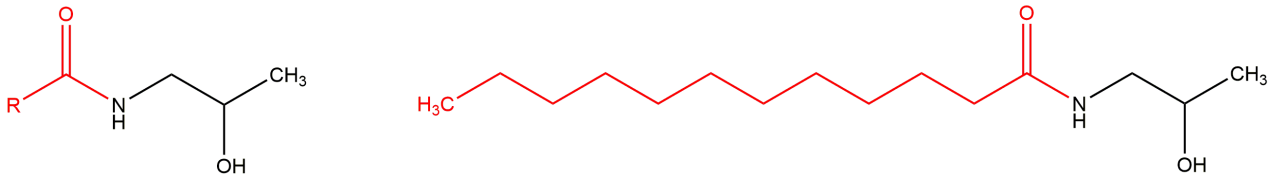


Figure 2. Alkyl amide MIPA ingredients (generic) and an example (Lauramide MIPA)

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.

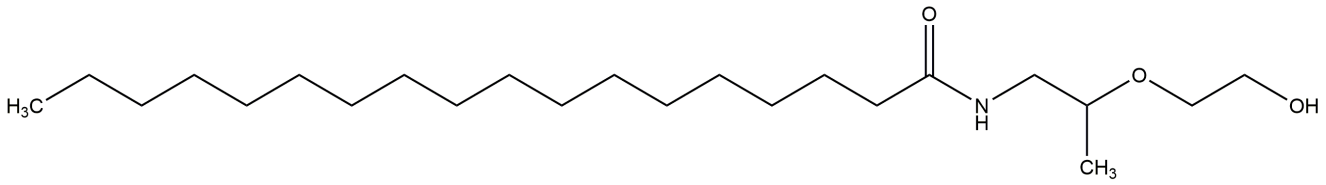


Figure 3. Hydroxyethyl Stearamide-MIPA

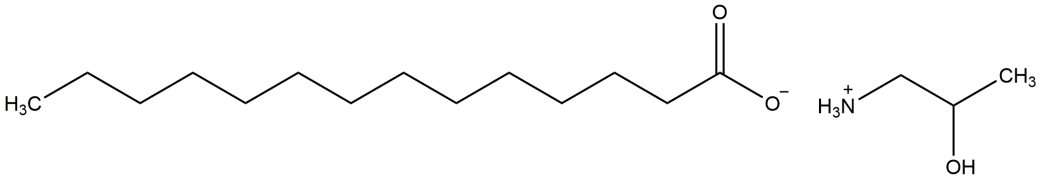


Figure 4. MIPA-Myristate

The definitions and structures of all the alkyl amide MIPA ingredients included in this report are provided in Table 1. The available fatty acid residue profiles for those ingredients derived from oils are available in Table 3.

Physical and Chemical Properties

The evaporation rate of Cocamide MIPA is estimated to be slower than that of ethyl ether.[20] 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 the ingredients in this report are provided in Table 4.

Method of Manufacture

Alkyl amide MIPA ingredients are generally manufactured by the reaction of a fatty acid source (i.e., free fatty acids; fatty acid methyl esters, or triglycerides) with MIPA at elevated temperatures.[21] The fatty acid source determines the alkyl chain distribution. Given the natural origin of fatty acids, the alkyl chains are even-numbered.

Impurities

Typical impurities/residues contained in alkyl amide MIPA ingredients are free MIPA (≤ 2%) and free fatty acid source (≤ 5%).[21] Glycerol (≤ 5%) may be present if triglycerides are used in feedstock.

Cocamide MIPA

Cocamide MIPA (96% minimum) contains monoisopropylamine (2% max) and methanol (< 1%).[20] In studies described later in this report, Cocamide MIPA (98.38% pure) was reported to contain 0.88% water and 0.74% free amine.[18,19]

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 (but not exclusively) used in rinse-off 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 use reported in 485 formulations.[22] Lauramide MIPA is most commonly used in bath soaps and detergents (453 formulations). Cocamide MIPA is reported to be used 335 cosmetic formulations, 324 of which are in rinse-off formulations. The results of the concentration of use surveys conducted by the Council in 2017 (updated in 2019)[23] and 2019 (for Peanutamide MIPA)[24] indicate that Cocamide MIPA has the highest maximum concentration of use, and is used at up to 12% in hair bleaches.[25] The next highest reported maximum concentration of use is 4.8% Lauramide MIPA in bath soaps and detergents. Oleamide MIPA was reported to only be used in hair dyes and colors according to VCRP data; however, the concentration of use reported in the Council survey was in face and neck products (up to 0.4%). This is the greatest (and only) maximum concentration of use for a dermal leave-on use reported for the alkyl amide MIPA ingredients. The frequency and concentration of use data for the alkyl amide MIPA ingredients are provided in Table 5, and 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%.[25]

Of the 14 alkyl amide ingredients named in the report, 12 are not restricted from use in any way under the rules governing cosmetic products in the European Union.[26] MIPA-Myristate is included in Annex III (List Of Substances Which Cosmetic Products Must Not Contain Except Subject to the Restrictions Laid Down; reference #61) under the category "monoalkylamines, monoalkanolamines and their salts;" this category of ingredients is included in the list of substances which cosmetic products must not contain, except subject to the restrictions and conditions laid down.[27] Accordingly, monoalkylamines, monoalkanolamines and their salts 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%; a maximum secondary amine content of 0.5% in raw materials; and a maximum nitrosamine content of 50 µg/kg. Additionally, Peanutamide MIPA is associated with reference #306 in Annex III, as a peanut oil extract/derivative; the maximum concentration of peanut protein allowed in peanut oil is 0.5 ppm.

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

Cocamide MIPA

The acute dermal LD_{50} of Cocamide MIPA was reported to be > 2000 mg/kg in rabbits.[20] (No details were provided.)

Isostearamide MIPA

The acute dermal toxicity of Isostearamide MIPA (100% pure) was determined using 5 male and 5 female HanIbm: WIST (SPF) rats in accordance with the Organization for Economic Cooperation and Development (OECD) test guideline (TG) 402.[18] Single semi-occlusive patches containing 2000 mg/kg Isostearamide MIPA (0.5 g/mL in PEG; 4 mL/kg) were applied for 24 h. No clinical signs were observed, and the LD_{50} was > 2000 mg/kg.

Oleamide MIPA

The acute dermal toxicity of Oleamide MIPA was determined using five female and five male Sprague-Dawley rats.[17] Rats were dermally administered 2000 mg/kg of Oleamide MIPA. The application site was covered by a semi-occlusive 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.

Cocamide MIPA (test substance - amides, C8-18 and C18-unsatd., N-(hydroxyethyl), for read-across, per ECHA)

In a limit test that was performed in a manner similar to OECD TG 402, a single application of 2000 mg/kg amides, C8-18 and C18-unsatd., *N*-(hydroxyethyl) in polyethylene glycol (PEG) was made to 5 male and 5 female Hanlbm:WIST (SPF) rats.[19] (Duration of the application and type of coverage was not stated.) The LD_{50} was > 2000 mg/kg.

Oral

Cocamide MIPA

The acute oral LD_{50} of Cocamide MIPA was reported to be > 2000 mg/kg in rats.[20] (No details were provided.)

Isostearamide MIPA

The acute toxicity of Isostearamide MIPA (94.1% pure) was determined according to OECD TG 401 using groups of 5 male and 5 female Sprague-Dawley rats.[18] The animals received a single dose of 2006 mg/kg bw by gavage (2.18 mL/kg bw), and the oral LD_{50} was determined to be > 2006 mg/kg bw.

Oleamide MIPA

An acute oral toxicity study was performed according to OECD TG 423.[17] 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.

Short-Term Toxicity Studies

Oral

Isostearamide MIPA

Groups of 5 male and 5 female Wistar rats were dosed by gavage with 0, 50, 200, or 1000 mg/kg bw/day Isostearamide MIPA in PEG 300 for 28 days in accordance with OECD TG 407.[18] An additional 5 rats/sex at the 0 and 1000 mg/kg bw/day were treated for 28 days, followed by a 14-day treatment-free recovery period to determine reversibility of effects. Clinical signs, food consumption, and body weights were recorded throughout the study. Functional observational battery, locomotor activity, and grip strength were performed during week 4. At the end of the dosing and the treatment-free recovery period, blood samples were withdrawn for hematology and plasma chemistry analyses. All animals were killed and necropsied; weights of several organs (including the testes) were determined. Microscopic examinations were performed on numerous organs (including the testes and ovaries) and tissues from all control and high dose animals, and on all gross lesions from all animals. Livers of animals of the low and mid-dose groups were examined to establish a no-effect level.

All animals survived until study termination. There were no effects on body weights. No test substance-related clinical signs were noted at any dose level, and no test substance-related clinical signs were evident in any animal of any group during the functional observational battery performed at week 4. Body weights and food consumption were unaffected by treatment. Salivation was noted in some of the high-dose animals; this finding was considered to be incidental. A statistically significant, test-article related, increase in absolute and relative liver weights of male and female high-dose animals was observed; this increase resolved after 2 wks of non-treatment. No treatment-related hematological findings were reported; some test article-related effects on clinical chemistry parameters were reported in the high-dose group. No gross lesions were reported at necropsy. Microscopically, test substance-related effects consisted of hepatocellular hypertrophy at minor degrees and hepatocellular cytoplasmic eosinophilia in both sexes treated with 1000 mg/kg bw/day; these effects were not observed in recovery animals. The no-observed-adverse-effect-level (NOAEL) was 200 mg/kg bw/day in male and female rats.

Cocamide MIPA (test substance - amides, C12-18 and C18-unsatd. N-(hydroxyethyl), for read-across, per ECHA)

A 28-day repeated dose study was performed in accordance with OECD TG 407 in which 0, 70, 250, and 750 (days 1 – 14)/1500 (days 15 - 28) mg/kg bw amides, C12-18 and C18-unsatd. *N*-(hydroxyethyl**)** in olive oil was administered by gavage 5 days/wk to groups of 10 male and 10 female Wistar rats.[19] Clinical signs, body weight, hematology, clinical chemistry, urinalysis, and gross and microscopic pathology were recorded. Additional groups of 5 male and 5 female rats were kept for a 4-mo recovery period. No mortalities were reported after dosing. No test article-related effects on organ weight were

observed. Dose-independent, reversible local findings were found in the forestomach mucosa of the high dose group. (Hyperplastic and cellular changes found in the forestomach were also found in controls.) The NOAEL was considered to be > 750 mg/kg bw.

Subchronic Toxicity Studies

Dermal

Cocamide MIPA and Isostearamide MIPA (test substance – amides, C8-18 and C18-unsatd., N,N-bis(hydroxyethyl), for read-across, per ECHA)

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 50, 100, 200, 400, or 800 mg/kg bw/day amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl) in ethanol by dermal application, 5 times/wk, for 14 weeks.[18] Mortality, clinical signs and body weights were recorded. At necropsy, gross effects were noted. Selected organs were weighed and a complete histopathological evaluation was performed on animals of the 0 and 800 mg/kg groups. All mice survived until the end of the study. The only treatment-related clinical finding was irritation of the skin at the site of application in males and females administered 800 mg/kg bw/day. There were no effects on body weight. Liver and kidney weights in 800 mg/kg males and females, liver weights of 400 mg/kg females, and lung weights of 800 mg/kg females were significantly increased compared to the controls. Histopathologic lesions of the skin at the site of application included epidermal hyperplasia, sebaceous gland hyperplasia, chronic active inflammation, parakeratosis and ulcer; the incidences and severities of these skin lesions generally increased with increasing dose in males and females. The NOAEL was considered to be 200 mg/kg bw/day for systemic effects and 100 mg/kg bw/day for local effects.

In a 14-wk dermal study following a similar protocol, groups of 10 male and 10 female Fischer 344 rats were exposed 5 times/wk to 0, 25, 50, 100, 200, or 400 mg/kg bw/day amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl) in ethanol.[18] All rats survived until the end of the study. Clinical findings included irritation of the skin at the site of application in males and females of the 100, 200, and 400 mg/kg dose groups. Final mean body weights and bodyweight gains of 200 and 400 mg/kg males and females were significantly lower than those of the controls. At week 14, a minimal microcytic, normochromic, non-responsive anemia occurred in the 100 and 200 mg/kg bw/day females and 400 mg/kg bw/day males and females. The anemia was also seen in the 400 mg/kg bw/day males and females on day 24. Increased segmented neutrophil counts occurred in 400 mg/kg bw/day males and females at week 14, and in 400 mg/kg bw/day females on day 24. Cholesterol concentrations were significantly decreased in 200 and 400 mg/kg bw/day males and in females administered 100 mg/kg or greater, and triglyceride concentrations were decreased in 200 and 400 mg/kg males. Histopathological lesions of the skin at the site of application included epidermal hyperplasia, sebaceous gland hyperplasia, chronic active inflammation, parakeratosis and ulcer; the incidence and severity of these skin lesions generally increased with increasing dose in males and females. The incidences of renal tubule regeneration in 100, 200, and 400 mg/kg bw/day females were significantly greater than in controls, and the severity in 200 and 400 mg/kg bw/day females was increased. The NOAELs for both systemic and local effects was 50 mg/kg bw/day in rats.

Oral

Oleamide MIPA

The subchronic toxicity of Oleamide MIPA was studied in a good laboratory practice (GLP)-compliant study performed in accordance with OECD TG 408.[17] 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 (ptyalism) and absence of spontaneous locomotor activity in the males. In another male, there was blood around and in the mouth. At 1000 mg/kg, there were ptyalism, chromodacryorrhea, dyspnea, bradypnea, absence of locomotor activity in the males and ptyalism 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 males treated with the test article at 100 mg/kg. There were 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 with 1000 mg/kg. There were higher liver weights noted in males and females and higher adrenal gland weights/lower thymus weights in males treated with 1000 mg/kg of the test article. There was no other change in organ weight in animals treated with 100 or 300 mg/kg and no mortality in the control group. The NOAEL was not determined in males. In females, the NOAEL corresponds to 300 mg/kg.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Dermal

Cocamide MIPA and Isostearamide MIPA (test substance - amides, C8-18 and C18-unsatd., N,N-bis(hydroxyethyl), for read-across, per ECHA)

In a 14-wk dermal toxicity study described above in which groups of 10 male and 10 female $B6C3F_1$ mice received open applications of 0 – 800 mg/kg bw amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl**)** in ethanol, 5 days/wk for 14 wks, samples were collected at the end of the study for sperm motility or vaginal cytology from mice of 200, 400, and 800 mg/kg bw groups.[18,19] The following sperm motility parameters were evaluated: spermatid heads per gram of testis, spermatid heads per testis, spermatid count, and epididymal spermatozoal motility and concentration. The left cauda epididymis, epididymis, and testis were weighed. Vaginal samples for cytology evaluations were collected for 12 consecutive days prior to the end of the studies from all female mice. The length of the estrous cycle and the length of time spent in each stage of the cycle were evaluated. Epididymal spermatozoal concentration was significantly increased in 800 mg/kg males. Estrous cycle lengths of dosed females were similar to that of the controls.

In the 14-wk dermal study described above in which groups of male and Fischer 344 rats received open applications, 5 days/wk, of 0 - 400 mg/kg bw amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl**)** in ethanol, sperm motility or vaginal cytology were collected at the end of the study from all rats receiving 100, 200, and 400 mg/kg bw of test material.[18,19] Test material results were similar to those of the vehicle controls.

Oral

Oleamide MIPA

In an oral developmental toxicity study performed in accordance 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.[17] On day 20 of gestation, all mated females were killed and necropsied, and all fetuses were examined. The clinical signs (ptyalism 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.

Another oral reproductive study was performed in accordance 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.[17] 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.

Cocamide MIPA and Isostearamide MIPA (test substance - amides, C12-18 (even-numbered) and C18-unsatd., N,N-bis(hydroxyethyl), for read-across, per ECHA)

Groups of 30 gravid female Sprague-Dawley CD rats were dosed by gavage with 0, 100, 300, and 1000 mg/kg bw/day amides, C12-18 (even-numbered) and C18-unsatd., *N,N*-bis(hydroxyethyl**)**, once daily on days 6 – 15 of gestation, in accordance with OECD TG 414.[18,19] Control animals were given vehicle alone (arachis oil, DAB 9). Clinical condition and reaction to treatment were recorded daily, and body weights were determined on days 0, 6, 16, and 20 of gestation. All surviving females were sacrificed on day 20 of gestation, and the fetuses were removed by caesarean section. At necropsy, the females were examined macroscopically. Live fetuses were weighed, sexed and examined for visceral and skeletal abnormalities. No deaths or treatment-related changes in body weight gain and necropsy findings were observed in dams at any dose level. Treatment-related symptoms observed in all groups were salivation and propulsion of the head. The highest dose group showed severe salivation. Apart from the control (1 dead fetus) and the 100 mg/kg bw/day groups (7 dead fetuses), all females had viable fetuses. Pre-implantation loss and mean numbers of resorptions were not affected by treatment. The data for post-implantation loss, embryonic deaths and total fetuses showed some deviations, which were considered to be non-treatment-related. Mean placental and uterine weights were not affected by dosing. Fetal sex ratio was comparable in all groups. No treatment-related fetal abnormalities were found at necropsy. The examined fetuses showed no treatment-related visceral and skeletal abnormalities/variations. One fetus of the 300 mg/kg group had a stump tail and missing coccygeal vertebrae. Further, the data for skeletal ossifications showed some deviations in the two highest dose groups. However, it was stated that all these

effects were assessed to be non-treatment-related. The NOAELs for parental toxicity and developmental toxicity were considered to be 1000 mg/kg bw/day.

GENOTOXICITY

The genotoxicity studies summarized below are presented in Table 7.[17-19]

Cocamide MIPA, Isostearamide MIPA, and Oleamide MIPA were not mutagenic in the Ames test, and Oleamide MIPA and amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl) (as read-across for Isostearamide MIPA, per ECHA) were not genotoxic in the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells. Cocamide MIPA and Oleamide MIPA were not clastogenic in the chromosomal aberration assay. However, Isostearamide MIPA was clastogenic in the chromosomal aberration assay in Chinese hamster lung fibroblasts. In vivo, Isostearamide MIPA was not genotoxic in a UDS assay in male Wistar rats or a micronucleus test in NMRI mice.

CARCINOGENICITY STUDIES

Dermal

Cocamide MIPA and Isostearamide MIPA (test substance - amides, C8-18 and C18-unsatd., N, N-bis(hydroxyethyl), for read-across, per ECHA)

Open applications of 0, 100, or 200 mg/kg bw of amides, C8-18 and C18-unsatd., *N*,*N*-bis(hydroxyethyl) in ethanol were made 5 days/wk to shaved skin of groups 50 male and 50 female B6C3F$_1$mice for 104 wks.[18] Survival of dosed males and 100 mg/kg bw females was similar to that of the vehicle controls; survival of the 200 mg/kg bw group of female mice was reduced compared to the vehicle control group, but the difference was not significant. Irritation was reported at the test site in males that received 200 mg/kg bw. Several nonneoplastic lesions of the skin at the application site were determined to be test article-related. Incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and hyperkeratosis in all dosed groups of males and females were significantly greater than those in the vehicle control groups, and the incidences of ulceration in 200 mg/kg bw males and inflammation and parakeratosis in 200 mg/kg bw females were increased. In the thyroid gland, the incidences of follicular cell hyperplasia in all dosed groups of males (vehicle control, 11/50; 100 mg/kg bw, 20/50; 200 mg/kg bw, 23/50) and females (27/50, 36/50, 33/50) were significantly greater than those in the vehicle controls. Follicular cell hyperplasia consisted of focal areas of thyroid gland follicles lined with increased numbers of epithelial cells, which formed papillary projections in some instances. Dosed male and female mice had significantly greater incidences of hepatic neoplasms (hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma (males) than the vehicle controls. There was a morphologic continuum from adenoma to carcinoma, with less differentiation and typical trabecular formations in the carcinomas. Carcinomas were often a centimeter or more in diameter, whereas adenomas were generally smaller and more discrete. Carcinomas metastasized to the lung in a few males and females. Adenomas, carcinomas, and hepatoblastomas displaced normal liver parenchyma, and none contained normal lobular architecture. Hepatoblastomas were characterized by well-demarcated focal areas composed of bundles of deeply basophilic, spindle-shaped cells. The incidences of renal tubule adenoma (1/50, 1/50, 7/50) and of renal tubule adenoma or carcinoma (combined) (1/50, 1/50, 9/50) in 200 mg/kg bw males were significantly greater than those in the vehicle controls. Renal tubule hyperplasia, adenoma, and carcinoma formed a morphological continuum. Adenomas were focal, compressive masses approximately five or more tubules in diameter; carcinomas were morphologically similar to adenomas but were larger and often showed cellular debris and/or mineralization. Renal tubule neoplasms were located in the cortex or outer medulla. Focal proliferative masses less than five tubules in diameter were classified as focal hyperplasia. It was stated there was clear evidence of carcinogenic activity in male B6C3F1 mice based on increased incidences of hepatic and renal tubule neoplasms and in female B6C3F1 mice based on increased incidences of hepatic neoplasms. The lowest-observable-adverse-effect-level (LOAEL) for systemic and local effects was considered to be 100 mg/kg bw/day.

In a 104-wk dermal study in rats, groups of 50 male and 50 female Fischer rats were exposed 5 days/wk to 0, 50, or 100 mg/kg bw/day of amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl**)** in ethanol.[18,19] Mortality, clinical signs and body weight were recorded throughout the study, and at necropsy, a gross macroscopic examination and complete histopathology were carried out. The survival rates of treated male and female rats were similar to those of controls. There were no significant differences in body weight throughout the groups. The only treatment-related clinical finding was irritation of the skin at the site of application in 100 mg/kg bw/day females. Non-neoplastic lesions of the skin at the site of application included epidermal hyperplasia, sebaceous gland hyperplasia, parakeratosis and hyperkeratosis; the incidences and severities of these lesions increased with increasing dose. There were marginal increases in the incidences of renal tubule adenoma or carcinoma (combined) in 50 mg/kg bw/day females. The severity of nephropathy increased with increasing dose in female rats. The incidences of chronic active inflammation, epithelial hyperplasia and epithelial ulcer of the forestomach increased with dose in female rats and the increases were significant in the 100 mg/kg bw/day group. There was no evidence of carcinogenic activity of the test substance in male rats at any dose; there was an equivocal evidence of carcinogenic activity in female rats based on a marginal increase in the incidences of renal tubule neoplasms. The NOAEL was considered to be 50 mg/kg bw/day in rats.

DERMAL IRRITATION AND SENSITIZATION

Irritation

In Vitro

Oleamide MIPA

The primary skin irritation potential of Oleamide MIPA was evaluated using the Episkin™ reconstructed human epidermis model based on OECD TG 439.[17] The test material (undiluted Oleamide MIPA; 10 mg) was applied to skin tissue. Oleamide MIPA was considered to be non-irritating to skin.

Animal

Isostearamide MIPA

Semi-occlusive patches containing 0.5 mL Isostearamide MIPA were applied for 4 h to a 6 cm^2 area of shaved skin of 3 male New Zealand White rabbits.[19] Erythema (scores 1.7 – 2 out of 4 max) was present until day 5; no edema was observed. Erythema decreased after day 5, and was resolved by day 8. Undiluted Isostearamide MIPA was not considered to be irritating to rabbit skin.

Cocamide MIPA (test substance - amides, C8-18 and C18-unsatd., N-(hydroxyethyl), for read across, per ECHA)

Occlusive patches containing 0.5 g amides, C8-18 and C18-unsatd., *N*-(hydroxyethyl) with 0.5 mL water were applied for 4 h to a 6 cm^2 area of shaved skin of 3 small white Russian rabbits.[19] Erythema, edema, and eschar were observed in all animals; the results were reversible within 14 days. The overall irritation score (24/48/72 h) was 3.67/8, and the test substance was considered to be moderately irritating.

Sensitization

Animal

Cocamide MIPA

A guinea pig maximization study was performed in accordance with OECD TG 406 to determine the sensitization potential of Cocamide MIPA.[19] Ten male Dunkin-Hartley guinea pigs were used in the test group, and 5 males were used as controls. Intradermal induction consisted of 3 injections: a 1:1 (v/v) mixture of Freund's Complete Adjuvant (FCA) and physiological saline; two injections of 5% Cocamide MIPA in bi-distilled water. Epidermal induction was performed after 1 wk (on day 8); an occlusive patch (2 cm x 4 cm) with 25% of the test substance in bi-distilled water was applied for 48 h to the clipped and shaved flanks of the test animals. After a 2 wk non-treatment period, on day 22, the challenge was performed by applying 2 cm x 2 cm occlusive patches containing 0.1 mL of 5% test material in bi-distilled water for 24 h; the test sites were evaluated 24 and 48 h after patch removal. 2-Mercaptobenzothiazole was used as a positive control; 70 % of the animals of the test group were observed with positive skin reactions after treatment with a non-irritant concentration of positive control (25 % v/v). All animals survived, and no clinical signs of toxicity were reported. "Normal local symptoms" were observed in test and control animals following intradermal induction. No erythema or edema were observed following epidermal induction. No positive reactions were reported following the challenge; the test material was not a sensitizer.

Isostearamide MIPA

A guinea pig maximization study was performed in accordance with OECD TG 406 to determine the sensitization potential of Isostearamide MIPA.[18] Ten male albino Himalayan guinea pigs were used in the test group, and 5 males were used as controls. Intradermal induction consisted of 3 injections: a 1:1 (v/v) mixture of FCA and physiological saline; 5% Isostearamide MIPA in bi-distilled water; and 5% Isostearamide MIPA in a 1:1 (v/v) mixture of FCA and physiological saline. Epidermal induction was performed after 1 wk (on day 8); 4 occlusive patches (3 cm x 3 cm) with 25, 50, 75, or 100% of the test substance (0.3 mL) were applied for 24 h to the clipped and shaved flanks of the test animals. After a 2 wk non-treatment period, the challenge was performed by applying 3 cm x 3 cm occlusive patches containing 0.2 mL of the vehicle or 1% test material in bi-distilled water for 24 h; the test sites were evaluated 24 and 48 h after patch removal. 2-Mercaptobenzothiazole was used as a positive control.

One animal of the test group was found dead on test day 10; no findings were noted at necropsy, and the death was considered to be spontaneous and not treatment related. The "expected and common findings" were observed in the control and test group after the different applications using FCA intradermally (on test day 1) and consisted of erythema, edema, necrotizing dermatitis, encrustation, and exfoliation of encrustation. After epidermal induction on day 8, discrete/patchy erythema was observed in all surviving test animals (treated group) at the 24 h reading after treatment with the undiluted test substance; these effects persisted in 1 animal at the 48-h reading. No reactions were observed in the negative controls. Following challenge (day 22), no skin reactions were observed in the test or the vehicle-control groups. The test substance was not considered to be a skin sensitizer.

Oleamide MIPA

The sensitization potential of Oleamide MIPA was evaluated in a guinea pig maximization study.[17] 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

Oleamide MIPA

The ocular irritation potential of Oleamide MIPA was evaluated in a bovine corneal opacity and permeability (BCOP) test performed in accordance with OECD TG 437.[17] 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

Isostearamide MIPA

Undiluted Isostearamide MIPA (94.1% pure; 0.1 mL) was instilled into the conjunctival sac of the left eye of 3 New Zealand White rabbits, and the contralateral eye served as an untreated control.[18] (Whether the eyes were rinsed was not stated.) Observations were made at 1, 24, 48, and 72 h. Some slight conjunctival reactions (chemosis with a score of ≤ 1 and enanthema with a score of 1 to 2) were observed in all rabbits after 1 h. Neither iris irritation nor corneal opacity were recorded. Reactions were fully reversible; no effects were seen at 24, 48, and 72 h. Under the study conditions, the test substance was not considered to be irritating to rabbit eye.

Oleamide MIPA

Three male New Zealand White rabbits were used to determine the ocular irritation potential of Oleamide MIPA.[17] 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.

Cocamide MIPA (test substance - amides, C8-18 and C18-unsatd., N-(hydroxyethyl), for read-across, per ECHA)

The ocular irritation potential of undiluted amides, C8-18 and C18-unsatd., *N*-(hydroxyethyl) was evaluated in 3 rabbits.[19] Ground test material (0.1 mL) was instilled into the conjunctival sac of the right eye; the contralateral eye served as a control. The mean overall score was 26.8/110, and the test substance was considered to be moderately irritating to rabbit eyes, and in one animal, irreversible effects (cornea, iris) occurred.

SUMMARY

This is a safety assessment of 14 alkyl amide MIPA ingredients as used in cosmetics. All of these ingredients are reported to function in cosmetics as a surfactant – foam booster and/or viscosity increasing agent; some of the ingredients have other reported functions. In some instances, information on substances used for read-across is provided to address data needs for certain toxicological endpoints. Specifically, information on amides, C8-18 and C18-unsatd., *N*-(hydroxyethyl) and amides, C12-18 and C18-unsatd, *N*-(hydroxyethyl) was used for read-across to Cocamide MIPA, and information on amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl) and amides, C12-18 (even-numbered) and C18-unsatd., *N,N*-bis(hydroxyethyl) was used for read-across for Cocamide MIPA and Isostearamide MIPA.

Four of the 14 ingredients included in this assessment are reported to be in use, according to the VCRP and/or the results of a Council survey. 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 only concentration of use reported resulting in leave-on dermal exposure is 0.4% Oleamide MIPA in face and neck preparations. Of the 14 alkyl amide ingredients named in the report, 12 are listed in the European Union inventory of cosmetic ingredients without restrictions; MIPA-Myristate is identified under the category monoalkylamines, monoalkanolamines and their salts, and restrictions

regarding amine and nitrosamine content apply. For Peanutamide MIPA, as a peanut oil extract/derivative, the maximum concentration of peanut protein allowed in peanut oil is 0.5 ppm.

The dermal LD_{50} of Cocamide MIPA is > 2000 mg/kg in rabbits (details not provided). In rats, the dermal LD_{50}s of Isostearamide MIPA and Oleamide MIPA (both ingredients, 24-h semi-occlusive patch) and of amides, C8-18 and C18-unsatd., *N*-(hydroxyethyl**)** in PEG (type and duration of patch not provided) were reported to be > 2000 mg/kg; these were the highest doses tested in each study. In acute oral studies in rats, the LD_{50}s for Cocamide MIPA, Isostearamide MIPA, and Oleamide MIPA were all reported to be > 2000 mg/kg; as with the dermal studies, these were the highest doses tested.

In a 28-day repeated-dose gavage study in rats with ≤ 1000 mg/kg bw/day Isostearamide MIPA, the NOAEL was 200 mg/kg bw, based on hepatic effects. Test substance-related effects consisted of hepatocellular hypertrophy at minor degrees and hepatocellular cytoplasmic eosinophilia in both sexes treated with 1000 mg/kg bw/day; these effects were not observed in 14-day recovery animals. In a 28-day study in which Wistar rats were dosed, 5 days/wk, with up to 1500 mg/kg amides, C12-18 and C18-unsatd. *N*-(hydroxyethyl) in olive oil by gavage, the NOAEL was considered to be > 750 mg/kg. In a 13-wk oral toxicity study in which male and female Sprague-Dawley rats were given ≤ 1000 mg/kg bw/day Oleamide MIPA in corn oil by gavage, mortality, low food consumption, and low body weight gain were reported in males. There were slight changes in the liver and the bone marrow in animals treated with test article at 1000 mg/kg. The NOAEL in females was determined to be 300 mg/kg bw/day Oleamide MIPA; a NOAEL was not determined for males.

In 14-wk dermal studies of amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl) in ethanol, open applications were made 5 days/wk to mice (≤ 800 mg/kg bw/day) and rats (≤ 400 mg/kg bw/day). The NOAELs for local and systemic effects in mice were 100 and 200 mg/kg bw, respectively, and in rats, the systemic NOAEL was 50 mg/kg bw. In both rats and mice, microscopic lesions of the skin at application site included epidermal hyperplasia, sebaceous gland hyperplasia, chronic active inflammation, parakeratosis and ulcer, with incidences and severities of these skin lesions generally increased with increasing dose in males and females.

As part of the 14-wk dermal toxicity studies described above, samples were collected at the end of the study for sperm motility or vaginal cytology. Epididymal spermatozoal concentration was significantly increased in male mice of the 800 mg/kg group; estrous cycle lengths of dosed female rats and mice were similar to controls.

In an oral developmental toxicity test in which groups of 20 mated female rats were dosed by gavage with up to 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, and the NOAEL was considered to be 1000 mg/kg/day. In a study in which groups of 30 gravid female Sprague-Dawley CD rats were administered up to 1000 mg/kg bw/day amides, C12-18 (even-numbered) and C18-unsatd., *N,N*-bis(hydroxyethyl) by gavage on days 6 – 15 of gestation, the NOAELs for parental toxicity and developmental toxicity were considered to be 1000 mg/kg bw/day.

The reproductive toxicity of Oleamide MIPA was evaluated in groups of 10 male and 10 female Sprague-Dawley rats at dose levels of ≤ 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 from 2 weeks before mating until day 5 post-partum (inclusive). No treatment-related, adverse effects were observed, and the NOAELs for parental toxicity, reproductive performance (mating and fertility), and toxic effects on progeny were 1000 mg/kg/day.

Cocamide MIPA, Isostearamide MIPA, and Oleamide MIPA were not mutagenic in the Ames test, and Oleamide MIPA and amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl**)** were not genotoxic in the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells. Cocamide MIPA and Oleamide MIPA were not clastogenic in the chromosomal aberration assay. However, Isostearamide MIPA was clastogenic in the chromosomal aberration assay in Chinese hamster lung fibroblasts, but at cytotoxic concentrations. In vivo, Isostearamide MIPA was not genotoxic in a UDS assay in male Wistar rats or a micronucleus test in NMRI mice.

Open applications of up to 200 mg/kg bw of amides, C8-18 (even-numbered) and C18-unsatd., *N*-(2-hydroxypropyl**)** in ethanol were made 5 days/wk to shaved skin of groups 50 male and 50 female $B6C3F_1$ mice for 104 wks; there was clear evidence of carcinogenic activity in male mice based on increased incidences of hepatic and renal tubule neoplasms and in female mice based on increased incidences of hepatic neoplasms. The LOAEL for systemic and local effects was considered to be 100 mg/kg bw/day. In a 104-wk dermal study in which groups of 50 male and 50 female Fischer rats were exposed 5 days/wk to up to 100 mg/kg bw/day of amides, C8-18 and C18-unsatd., *N, N*-bis(hydroxyethyl) in ethanol, there was no evidence of carcinogenic activity of the test substance in male rats at any dose; there was an equivocal evidence of carcinogenic activity in female rats based on a marginal increase in the incidences of renal tubule neoplasms. The NOAEL was considered to be 50 mg/kg bw/day in rats.

In an Episkin™ reconstructed human epidermis assay, Oleamide MIPA was determined to be a non-irritant to skin. A 4-h semi-occlusive application of undiluted Isostearamide MIPA was not considered to be irritating to rabbit skin. However, in another study, a 4-h occlusive patch of amides, C8-18 and C18-unsatd., *N*-(hydroxyethyl) was moderately irritating to rabbit skin.

Neither Cocamide MIPA (epidermal induction and challenge with 5%) or Isostearamide MIPA (epidermal induction with 25 - 100%, challenge with 1%) were sensitizers in the guinea pig maximization test. However, in a guinea pig maximization test in which 10% Oleamide MIPA in corn oil was used for intradermal induction, 75% Oleamide MIPA in ethanol/water was used for topical induction, and 50% Oleamide MIPA was used at challenge, delayed contact hypersensitivity was reported in in more than 30% of the 20 test animals.

The ocular irritation potential of Oleamide MIPA was evaluated in vitro using a BCOP study; an irritancy score of 2.0 was reported, and it was concluded that the Oleamide MIPA is not an ocular corrosive or severe irritant. In rabbits, undiluted Isostearamide MIPA and Oleamide MIPA were non-irritating to rabbit eyes, but amides, C8-18 and C18-unsatd., *N*-(hydroxy-ethyl) was a moderate ocular irritant.

DISCUSSION

The ingredients in this group are fatty amides resulting from amidation with MIPA. Accordingly, the Panel specified that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

The alkyl amide MIPA ingredients are primarily used in rinse-off formulations. However, leave-on uses are reported, with 0.4% Oleamide MIPA reported as the highest maximum concentration of use for leave-on dermal exposure. The Panel noted that delayed contact hypersensitivity was reported in a GPMT performed with high concentrations of Oleamide MIPA (75% for topical induction/50% at challenge), but not in GPMTs on Cocamide MIPA (25% at topical induction/5% at challenge) and Isostearamide MIPA (100% at topical induction/1% at challenge). The Panel stated that the sensitization observed with Oleamide MIPA was most likely a result of the high concentrations and a stressing of the system (as this method of testing utilizes a combination of exposures, including intradermal injections which bypass the stratum corneum). Because the Panel felt that it was appropriate to read-across from Cocamide MIPA and Isostearamide MIPA, concern that Oleamide MIPA would be a sensitizer in cosmetic formulations was mitigated. However, the Panel was concerned that the potential exists for dermal or ocular irritation with the use of products formulated with the ingredients named in this assessment. Therefore, the Panel specified that products containing alkyl amide MIPA ingredients must be formulated to be non-irritating.

Published studies were not found, and unpublished data were not submitted, for certain toxicological endpoints on the alkyl amide MIPA ingredients. The Panel determined that the data on similar substances provided in ECHA dossiers could be used for read-across for the missing data endpoints. The Panel noted adverse effects observed in the 14-wk dermal studies in mice and rats on the read-across test substance (C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl)); however, the adverse effects reported were at concentrations above what is reported to be used in cosmetic formulations, thereby mitigating any concerns for dermal toxicity. The same reasoning was used to mitigate concerns for positive results that were observed in the dermal carcinogenicity study that same read-across test substance in mice; furthermore, positive results were not observed in a dermal carcinogenicity study on the same test compound in rats. Additionally, the Panel stated that the CIR safety assessment of diethanolamides also supported the safety of the alkyl amide MIPA ingredients because of the structural similarities between the ingredients.

The acyl groups (i.e. fatty acid chain residues) in Peanutamide MIPA are derived from peanut oil. The Panel has previously reviewed the safety of Arachis Hypogaea (Peanut) Oil as used in cosmetics, and discussed therein the relationship between food allergies and exposure to refined oils. Individuals who have food allergies to a plant protein rarely exhibit allergic reactions when exposed to refined oils of the same plant; proteins do not partition into the oil. Additionally, the Panel noted that aflatoxins, which could be associated with peanuts, do not partition into the oil. However, the Panel does caution manufacturers to make certain that Peanutamide MIPA is free from proteins and aflatoxins.

CONCLUSION

The CIR Expert Panel concluded that the 14 alkyl amide MIPA ingredients listed below are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

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

**Use not reported in the VCRP and/or concentration of use survey. The expectation is that if used in cosmetic formulations, these ingredients would be used in product categories and at concentrations comparable to that reported for others in this group.*

TABLES

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

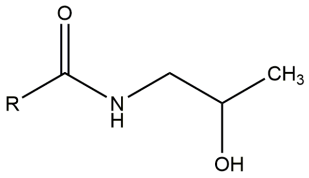
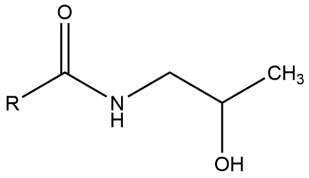
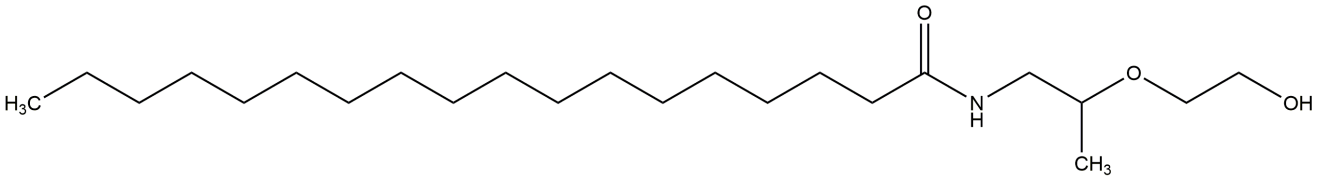
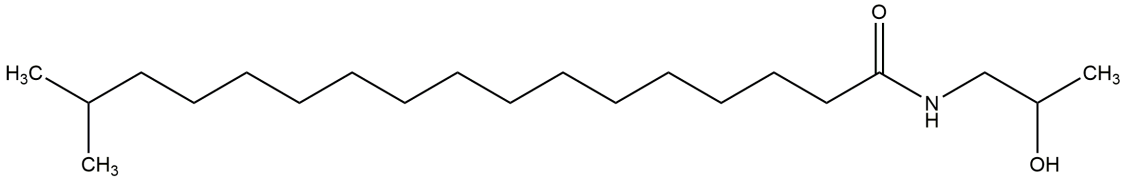
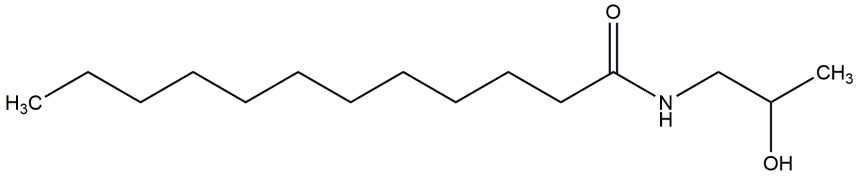
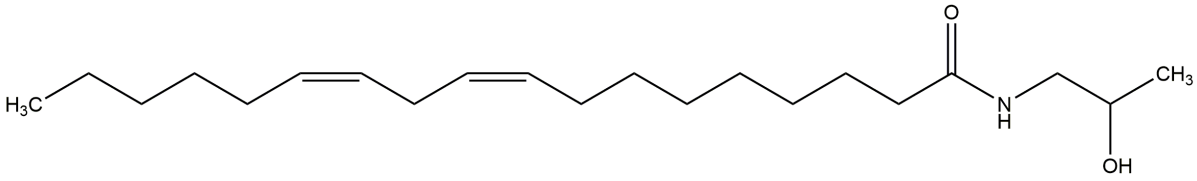
Ingredient & CAS No.	Definition & Example Structure	Function(s)
Cocamide MIPA 68333-82-4; 1335203-30-9 (generic)	Cocamide MIPA s the organic compound that conforms generally to the formula:  wherein RC(O)- represents the acyl groups derived from Cocos Nucifera (Coconut) Oil	surfactant - foam booster; viscosity increasing agent - 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 agent - nonaqueous
Hydroxyethyl Stearamide-MIPA	Hydroxyethyl Stearamide-MIPA is the substituted isopropanolamide that conforms generally to the formula: 	opacifying agent; viscosity increasing agent - aqueous
Isostearamide MIPA 170573-32-7; 152848-22-1	Isostearamide MIPA is the organic compound that conforms to the formula: 	surfactant - foam booster; viscosity increasing agent – aqueous
Lauramide MIPA 142-54-1	Lauramide MIPA is the organic compound that conforms to the formula: 	surfactant - foam booster; viscosity increasing agent - aqueous
Linoleamide MIPA	Linoleamide MIPA is the organic compound that conforms to the formula: 	hair conditioning agent; surfactant - foam booster; viscosity increasing agent – aqueous

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

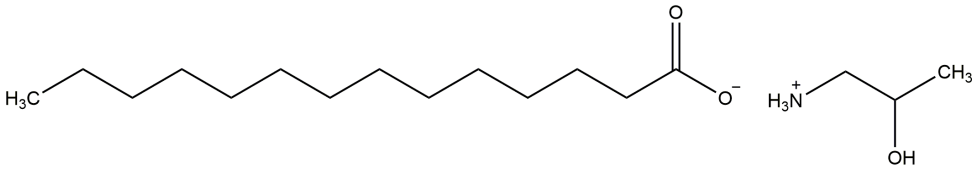
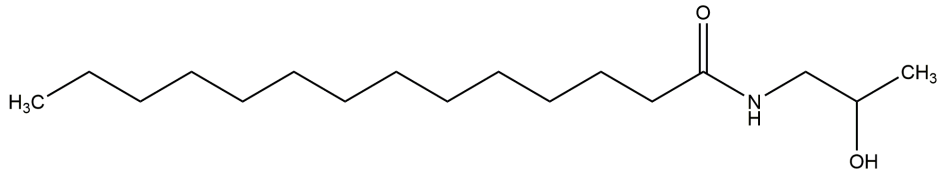
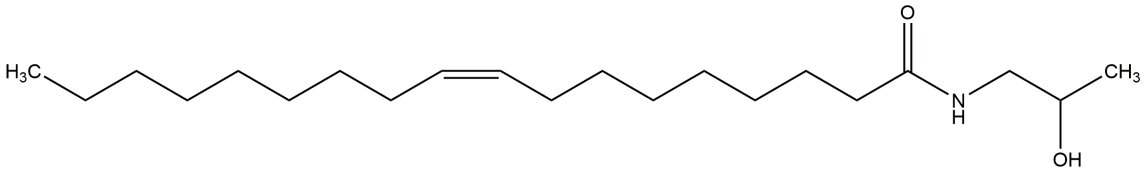
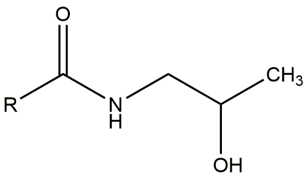
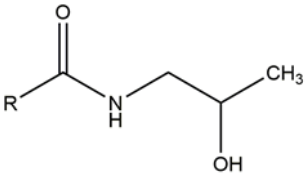
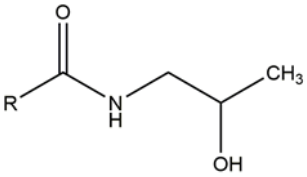
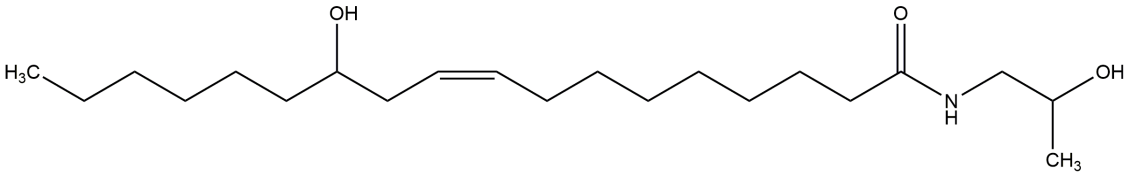
Ingredient & CAS No.	Definition & Example Structure	Function(s)
MIPA-Myristate	MIPA-Myristate is the salt of monoisopropanolamine and myristic acid. It conforms to the formula: 	surfactant - foam boosters; viscosity increasing agent - aqueous
Myristamide MIPA 10525-14-1	Myristamide MIPA is the organic compound that conforms to the formula: 	surfactant - foam booster; viscosity increasing agent – aqueous
Oleamide MIPA 111-05-7; 54375-42-7	Oleamide MIPA is the organic compound that conforms to the formula: 	surfactant - foam booster; viscosity increasing agent - aqueous
Palmamide MIPA	Palmamide is the organic compound that conforms to the formula:  wherein RC(O)- represents the acyl groups derived from palm oil.	surfactant - foam booster; viscosity increasing agent - aqueous
Palm Kernelamide MIPA 1335203-30-9 (generic)	Palm Kernelamide MIPA is the organic compound that conforms to the formula:  wherein RC(O)- represents the acyl groups derived from palm kernel oil.	surfactant - foam booster; viscosity increasing agent - aqueous
Peanutamide MIPA	Peanutamide MIPA is the organic compound that conforms to the formula:  wherein RC(O)- represents the acyl groups derived peanut oil.	surfactant - foam booster; viscosity increasing agent - aqueous
Ricinoleamide MIPA 40986-29-6	Ricinoleamide MIPA is the organic compound that conforms to the formula: 	surfactant - foam booster; viscosity increasing agent - 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)
Stearamide MIPA 35627-96-4	Stearamide MIPA is the organic compound that conforms to the formula:	surfactant - foam booster; viscosity increasing agent - aqueous

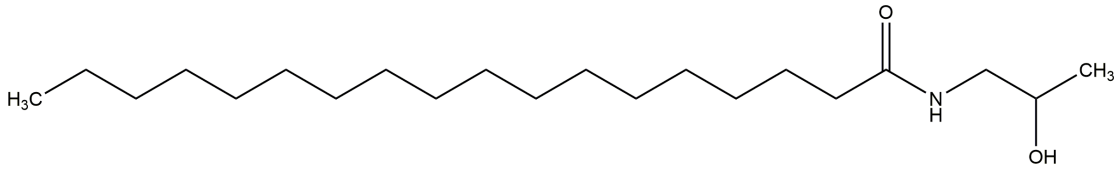


Table 2. CIR Conclusions of Components of the Alkyl Amide MIPA Ingredients that were Previously Reviewed

Component Reviewed	Conclusion (Most Recent)	Assessment Publication Status	Reference
Arachis Hypogaea (Peanut) Oil	safe as used	published in 2001; included in plant-derived fatty acid oils report published in 2017	15 10
Coconut Acid	safe as used	published in 1986; re-review published in 2011; included in plant-derived fatty acid oils report published in 2017	14 9 10
Cocos Nucifera (Coconut) Oil	safe as used	published in 1986; re-review published in 2011; included in plant-derived fatty acid oils report published in 2017	14 9 10
Elaeis Guineensis (Palm) Oil	safe as used	published in 2000; included in plant-derived fatty acid oils report published in 2017	4 10
Elaeis Guineensis (Palm) Kernel Oil	safe as used	published in 2000; included in plant-derived fatty acid oils report 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 when formulated to be non-irritating and non-sensitizing, which may be based on a QRA	published in 1983; re-review published in 2005 – not reopened; included in fatty acids and fatty acid salts report finalized in 2019	12 6 11
Lauric Acid	safe as used when formulated to be non-irritating and non-sensitizing, which may be based on a QRA	published in 1987; re-review published in 2006 – not reopened; included in fatty acids and fatty acid salts report finalized in 2019	13 7 11
Linoleic Acid	safe as used when formulated to be non-irritating and non-sensitizing, which may be based on a QRA	included in fatty acids and fatty acid salts report finalized in 2019	11
Myristic Acid	safe as used when formulated to be non-irritating and non-sensitizing, which may be based on a QRA	published in 1987; re-review published in 2006 – not reopened; included in expanded report with salts and esters published in 2010; included in fatty acids and fatty acid salts report finalized in 2019	13 7 8 11
Oleic Acid	safe as used when formulated to be non-irritating and non-sensitizing, which may be based on a QRA	published in 1987; re-review published in 2006 – not reopened; included in fatty acids and fatty acid salts report finalized in 2019	13 7 11
Ricinoleic Acid	safe as used	published in 2007	5
Stearic Acid	safe as used when formulated to be non-irritating and non-sensitizing, which may be based on a QRA	published in 1987; re-review published in 2006 – not reopened; included in fatty acids and fatty acid salts report finalized in 2019	13 7 11

Table 3. **Fatty acid composition (%) of component 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
	Cocamide MIPA	
Physical Form	solid; pastilles	[20]
Color	white	[20]
Melting Point/Freezing Point (°C)	52.22	[20]
Initial Boiling Point (°C)	150	[20]
	Hydroxyethyl Stearamide-MIPA	
Molecular Weight (g/mol)	385.6	[28]
	Isostearamide MIPA	
Physical Form	yellow liquid to paste	[18]
Molecular Weight (g/mol)	341.58	[29]
Density (g/mL @ 50°C)	0.988	[18]
Freezing Point (°C)	8	[18]
Boiling Point (°C)	decomposed	[18]
Water Solubility (mg/L)	8.5	[18]
log P_{ow} (@ 20°C)	≥ 3.3 to ≤ 7	[18]
	Lauramide MIPA	
Molecular Weight (g/mol)	257.418	[30]
Density/Specific Gravity (@ 20ºC)	0.919 ± 0.06	[23]
Melting Point (ºC)	65 – 66	[23]
Boiling Point (ºC)	418.3 ± 28.0	[23]
Dissociation constant; (pK_a; @25ºC)	14.56 ± 0.20	[23]
	Linoleamide MIPA	
Molecular Weight (g/mol)	337.6	[28]
	Myristamide MIPA	
Molecular Weight (g/mol)	285.472	[31]
Molecular Volume (mL/mol)	312.9 ± 3.0	[23]
Formula Weight	303.5	[28]
Density (@ 20ºC)	0.912 ± 0.06	[23]
Vapor Pressure (@ 25ºC)	9.44×10^{-10}	[23]
Melting Point (ºC)	70 – 72	[23]
Boiling Point (ºC)	444.1 ± 28.0	[23]
Dissociation constant (pK_a; @25ºC)	14.56 ± 0.20	[23]
	Oleamide MIPA	
Physical Form	Paste	[17]
Color	Beige	[17]
Odor	Strong	[17]
Molecular Weight (g/mol)	339.564	[32]
Density/Specific Gravity (g/mL @ 25ºC)	0.883, 0.891	[17]
Vapor pressure (25ºC)	0	[17]
Melting Point (ºC)	35.9 - 41.7	[17]
Boiling Point (ºC)	503.6 ± 43.0	[23]
Water Solubility (mg/L)	1	[17]
log K_{ow}	6.39	[17]
	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)	5.15×10^{-14}	[23]
Boiling Point (ºC)	542.1 ± 40.0	[23]
Dissociation constant (pK_a, @25ºC)	14.51 ± 0.10	[23]
	Stearamide MIPA	
Molecular Weight (g/mol)	341.57	[23]
Molecular Volume (mL/mol)	378.9 ± 3.0	[23]
Density (@ 20ºC)	0.901 ± 0.06	[23]
Vapor pressure (@ 25ºC)	8.03×10^{-12}	[23]
Boiling Point (ºC)	493.8 ± 28.0	[23]
Dissociation constant (pK_a; @25ºC)	14.56 ± 0.20	[23]

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

	# of Uses[22]	Max Conc of Use (%)[23]	# of Uses[22]	Max Conc of Use (%)[23]	# of Uses[22]	Max Conc of Use (%)[23]
	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*	*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)[22-24]

Coconut Oil MIPA Amides
Hydroxyethyl Stearamide MIPA
Linoleamide MIPA
Myristamide MIPA
Palmamide MIPA
Palm Kernelamide MIPA
Peanutamide MIPA
Ricinoleamide MIPA
Stearamide MIPA
MIPA-Myristate

Table 7. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
Cocamide MIPA	3 - 5000 µg/plate	deionized water	*Salmonella typhimurium* TA1535, TA1537, TA98 and TA100	Ames test, with and without metabolic activation	non-mutagenic	[19]
Cocamide MIPA (98.38% pure)	test 1: 0.1 - 45 µg/mL without S9; 1 - 250 µg/mL with 8% (v/v) S9-mix test 2: 0.1 - 35 µg/mL without S9; 1 - 200 µg/mL with 12% (v/v) S9-mix	DMSO	mouse lymphoma L5178Y cells	mammalian cell gene mutation assay Exposure duration: 3 h (Experiment 1), 24 and 48 h (Experiment 2 without S9 mix) and 3 h (Experiment 2 with S9 mix)	not genotoxic with or without metabolic activation	[19]
Cocamide MIPA (98.38% pure)	experiment 1: 50 – 300 µg/mL, 3 h exposure, with and without metabolic activation experiment 2: 10 – 300 µg/mL, 24 h exposure, without activation; 10 – 200 µg/mL, 48 h exposure, without activation; 50 – 300 µg/mL, 3 h exposure, with activation	DMSO	cultured peripheral human lymphocytes	mammalian chromosome aberration test	not clastogenic with or without metabolic activation	[19]
Isostearamide MIPA (94.1% pure)	(incorporation test: 33 - 5000 µg/plate pre-incubation test: 42 - 5000 µg/plate	DMSO or deionized water	*S. typhimurium* TA1535, TA1537, TA98 and TA100; *Escherichia coli* WP2 uvr A	Ames test, with and without metabolic activation	not mutagenic	[18]
Isostearamide MIPA	0, 20.3, 40.6, 81.3, 162.5, 325, 650, 1700 and 3400 µg/mL	DMSO	Chinese hamster lung fibroblasts (V79)	chromosomal aberration assay; Experiment 1: 4-h incubation, with and without metabolic activation; negative and positive controls were used Experiment 2: 4-h exposure period with metabolic activation; 18 and 28 h exposure without metabolic activation	clastogenic Clear toxic effects were observed after treatment with ≥40.6 µg/mL with and without metabolic activation; 24h continuous treatment with 20.3 µg/mL and above in the absence of S9 mix induced strong toxic effects Experiment I: strongly reduced mitotic indices (24% of control) after 4 h treatment with 40 µg/mL without activation; the aberration rate of the cultures treated with 20 µg/mL of the test substance was statistically significant Experiment II: the mitotic indices were reduced after continuous treatment with 20 µg/mL (18 h interval: 55.1% of control; 28 h interval: 75.3% of control) without activation. With activation, the mitotic index was reduced after treatment with 60 µg/mL (28 h interval: 52.8% of control). Without activation, no significant increase was observed in the aberration rates at any of the experimental time points	[18]

Table 7. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
Isostearamide MIPA (test substance - amides, C8-18 and C18-unsatd., *N,N*-bis(hydroxyethyl), for read-across, per ECHA)	test 1: 0.1 - 45 µg/mL without S9; 1 - 250 µg/mL with 8% (v/v) S9-mix test 2: 0.1 - 35 µg/mL without S9; 1 - 200 µg/mL with 12% (v/v) S9-mix	DMSO	mouse lymphoma L5178Y cells	mammalian cell gene mutation assay Exposure duration: 3 h (Experiment 1), 24 and 48 h (Experiment 2 without S9 mix) and 3 h (Experiment 2 with S9 mix)	not genotoxic with or without metabolic activation	[18]
Oleamide MIPA	all strains: up to 5000 µg/plate, without activation with activation, TA1535, up to 500 µg/plate, and strains TA100 and TA102 up to 5000 µg/plate	ethanol	*S. typhimurium* TA1535, TA1537, TA98, TA100, and TA102	Ames test, with and without metabolic activation; three or four independent assays; 2000 mononucleated cells were evaluated per concentration	not mutagenic	[17]
Oleamide MIPA	0.05 – 0.20 mM, without activation, 3-h treatment 0.075 – 0.40 mM with activation	ethanol	TK6 lymphoblastoid human cells	chromosomal aberration assay, in accordance with OECD TG 487	induced no biologically or statistically significant increase in the micronucleated cells with or without metabolic activation	[17]
Oleamide MIPA	0.056 – 0.150 mM, without S9, 3-h treatment. 0.020 – 0.080 mM, without metabolic activation 24-hour treatment 0.075 – 0.3 mM, with S9 0.075 – 0.175 mM	ethanol	L5178Y mouse lymphoma	gene mutation assay, in accordance with OECD TG 476	not mutagenic	[17]
IN VIVO						
Isostearamide MIPA (94.1% pure)	0, 500 or 2000 mg/kg bw for 2 or 16 h	0.5% CMC in deionized water	male Wistar rats	UDS, in accordance with OECD TG 486; single oral dose by gavage	not genotoxic	[18]
Isostearamide MIPA (94.1% pure)	200, 670, or 2000 mg/kg bw	corn oil	male/female NMRI mice	micronucleus assay; single oral dose by gavage	not genotoxic	[18]

Abbreviations: CMC – carboxymethylcellulose; DMSO – dimethyl sulfoxide; UDS – unscheduled DNA synthesis

REFERENCES

1. Nikitakis J, Kowcz A. Web-Based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*). http://webdictionary.personalcarecouncil.org/jsp/IngredientSearchPage.jsp. Washington, D.C.: Personal Care Products Council. Last Updated: Accessed: 8/21/2019.

2. Elder RL (ed.). Final report on the safety assessment of diisopropanolamine, triisopropanolamine, isopropanolamine, and mixed isopropanolamine. *J Am Coll Toxicol*. 1987;6(1):53-76.

3. Andersen FA (ed.). Annual Review of Cosmetic Ingredient Safety Assessments-2004/2005. *Int J Toxicol*. 2006;25(Suppl 2):23-28.

4. Andersen FA (ed.). Final Report on the Safety Assessment of Elaeis Guineensis (Palm) Oil, Elaeis Guineensis (Palm) Kernel Oil, Hydrogenated Palm Oil, and Hydrogenated Palm Kernel Oil. *Int J Toxicol*. 2000;19(Suppl 2):7-28.

5. Andersen FA (ed.). Final Report on the Safety Assessment of Ricinus Communis (Castor) Seed Oil, Hydrogenated Castor Oil, Glyceryl Ricinoleate, Glyceryl Ricinoleate SE, Ricinoleic Acid, Potassium Ricinoleate, Sodium Ricinoleate, Zinc Ricinoleate,Cetyl Ricinoleate, Ethyl Ricinoleate, Glycol Ricinoleate, Isopropyl Ricinoleate, Methyl Ricinoleate, and Octyldodecyl Ricinoleate. *Int J Toxicol*. 2007;26(Suppl 3):31-77.

6. Andersen FA (ed.). Annual Review of Cosmetic Ingredient Safety Assessments - 2002/2003. *Int J Toxicol*. 2005;24(Suppl 1):55-56.

7. Andersen FA (ed.). Annual Review of Cosmetic Ingredient Safety Assessments - 2004/2005. *Int J Toxicol*. 2006;25(Suppl 2):40-47.

8. Becker LC, Bergfeld WF, Belsito DV, et al. Final Report of the Amended Safety Assessment of Myristic Acid and Its Salts and Esters as Used in Cosmetics. *Int J Toxicol*. 2010;29(Suppl 3):162S-186S.

9. Burnett CL, Bergfeld WF, Belsito DV, et al. Final Report on the Safety Assessment of *Cocos nucifera* (Coconut) Oil and Related Ingredients. *Int J Toxicol*. 2011;30(Suppl 1):5S-16S.

10. Burnett CL, Fiume MM, Bergfeld WF, et al. Safety Assessment of Plant-Derived Fatty Acid Oils as Used in Cosmetics. *Int J Toxicol* 2017;36(Suppl 3):51S-129S.

11. Burnett CL, Bergfeld WF, Belsito DV, et al. 2019. Safety Assessment of Fatty Acids and Fatty Acid Salts as Used in Cosmetics (Final Report). Available from CIR. https://www.cir-safety.org/ingredients

12. Elder RL (ed.). Final Report on the Safety Assessment of Isostearic Acid. *J Am Coll Toxicol*. 1983;2(7):61-74.

13. Elder RL (ed.). Final Report on the Safety Assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid. *J Am Coll Toxicol*. 1987;6(3):321-401.

14. Elder RL (ed.). Final Report on the Safety Assessment of Coconut Oil, Coconut Acid, Hydrogenated Coconut Acid, and Hydrogenated Coconut Oil. *J Am Coll Toxicol*. 1986;5(3):103-121.

15. Andersen FA (ed.). Final Report on the Safety Assessment of Peanut (Arachis Hypogaea) Oil, Hydrogenated Peanut Oil, Peanut Acid, Peanut Glycerides, and Peanut (Arachis Hypogaea) Flour. *Int J Toxicol*. 2001;20(2):65-77.

16. Fiume MM, Heldreth BA, Bergfeld WF, et al. Safety Assessment of Diethanolamides as Used in Cosmetics. *Int J Toxicol*. 2013;32(Suppl 1):36S-58S.

17. European Chemical Agency (ECHA). REACH dossier: N-(2-hydroxypropyl)oleamide (CAS 111-05-7; Oleamide MIPA). https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/10994. Last Updated: 7/14/2019. Accessed: 8/21/2019.

18. European Chemical Agency (ECHA). REACH dossier: isostearic acid monoisopropanolamide (Isostearamide MIPA). https://echa.europa.eu/en/registration-dossier/-/registered-dossier/2879. Last Updated: 10/10/2017. Accessed: 8/21/2019. Note: The test material was not always clearly defined in the dossier; however, personal communication with the C. Eisenmann (May 6, 2019) provided confirmation that the test article identified as "constituent" with lot number E16734, purity 94.1%, is Isostearamide MIPA.

19. European Chemical Agency (ECHA). REACH dossier: Amides, C8-18 (even-numbered) and C18 (unsatd.), N-(2-hydroxypropyl) (CAS No. 1335203-30-9). https://echa.europa.eu/registration-dossier/-/registered-dossier/13560. Last Updated: 08/17/2019. Accessed: 08/21/2019.

20. Anonymous. 2018. Summary information: Cocamide MIPA. Unpublished data submitted by the Personal Care Products Council on March 22, 2019.

21. Anonymous. 2019 2019. Method of manufacture of MIPA fatty acid alkanolamides. Unpublished data submitted by the Personal Care Products Council on March 28, 2019.

22. U.S. Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. 2019 2019. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3, 2019; received February 13, 2019.

23. Personal Care Products Council. 2019. Updated Use Information: Alkyl Amide MIPA ingredients. Unpublished data submitted by Personal Care Products Council on August 29, 2019; data were originally collected in 2017. .

24. Personal Care Products Council. 2019. Peanutamide MIPA - concentration of use Unpublished data submitted by the Personal Care Products Council on July 23, 2019.

25. Personal Care Products Council. 2017. Concentration of Use by FDA Product Category: Alkyl Amide MIPA. Unpublished data submitted by Personal Care Products Council on September 28, 2017.

26. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated: Accessed: 02/08/2019.

27. European Commission. European Commission (EC). Annex III; List of substances which cosmetic products must not contain except subject to the restrictions laid down. http://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex%20III_v2.pdf. Last Updated: 5/8/2019. Accessed: 8/21/2019.

28. PerkinElmer Informatics. ChemDraw Pro. Version 18. 2018.

29. US National Library of Medicine (NLM). National Center for Biotechnology Information. PubChem Compound Database: Isostearamide MIPA; CID=15825518,. http://pubchem.ncbi.nlm.nih.gov/compound/15825518#section=Chemical-and-Physical-Properties. 2018. Accessed: 9/6/2018.

30. US National Library of Medicine (NLM). National Center for Biotechnology Information. PubChem Compound Database: Lauramide MIPA; CID=9903249,. http://pubchem.ncbi.nlm.nih.gov/compound/9903249#section=Chemical-and-Physical-Properties. 2018. Accessed: 9/6/2018.

31. US National Library of Medicine (NLM). National Center for Biotechnology Information. PubChem Compound Database: Myristamide MIPA; CID=111657,. http://pubchem.ncbi.nlm.nih.gov/compound/111657#section=Chemical-and-Physical-Properties. 2018. Accessed: 9/6/2018.

32. US National Library of Medicine (NLM). National Center for Biotechnology Information. PubChem Compound Database: Oleamide MIPA; CID=6436066,. http://pubchem.ncbi.nlm.nih.gov/compound/6436066#section=Chemical-and-Physical-Properties. 2018. Accessed: 9/6/2018.

Article

International Journal of Toxicology
32(Supplement 1) 36S-585

DOI: 10.1177/1091581813486300
ijt.sagepub.com
SAGE

Safety Assessment of Diethanolamides as Used in Cosmetics

Monice M. Fiume[1], Bart Heldreth[2], Wilma F. Bergfeld[3], Donald V. Belsito[3], Ronald A. Hill[3], Curtis D. Klaassen[3], Daniel C. Liebler[3], James G. Marks Jr[3], Ronald C. Shank[3], Thomas J. Slaga[3], Paul W. Snyder[3] and F. Alan Andersen[4]

Abstract

Cocamide diethanolamine (DEA) and some of the other diethanolamides are mainly used as surfactant foam boosters or viscosity increasing agents in cosmetics, although a few are reported to be used as hair and skin conditioning agents, surfactant-cleansing or surfactant-emulsifying agents, or as an opacifying agent. The Cosmetic Ingredient Review (CIR) Expert Panel considered new data and information from previous CIR reports to assess the concerns about the potential for amidases in human skin to convert these diethanolamides into DEA and the corresponding fatty acids. The Expert Panel concluded that these diethanolamides are safe as used when formulated to be nonirritating and when the levels of free DEA in the diethanolamides do not exceed those considered safe by the Panel. The Panel also recommended that these ingredients not be used in cosmetic products in which N-nitroso compounds can be formed.

Keywords

diethanolamides, cocamide DEA

The Cosmetic Ingredient Review (CIR) Expert Panel reviewed the available safety information of Cocamide diethanolamine (DEA) and an additional 32 diethanolamides. Cocamide DEA was previously reviewed in 1996, with the conclusion that this particular diethanolamide is safe when used in rinse-off products and safe at concentrations $\leq$10% in leave-on cosmetic products, and that cocamide DEA should not be used as an ingredient in cosmetic products in which N-nitroso compounds are formed.[1] Cocamide DEA had been originally reviewed in 1986.[2]

Because the data on Cocamide DEA and other available information on tertiary amides reviewed are similar, the Panel determined that the data are sufficient to support the safety of the entire group, and the following 33 diethanolamides are included in this review:

Almondamide DEA
Apricotamide DEA
Avocadamide DEA
Babassuamide DEA
Behenamide DEA
Capramide DEA
Cocamide DEA
Cornamide DEA
Cornamide/Cocamide DEA
Hydrogenated Tallowamide DEA
Isostearamide DEA
Lanolinamide DEA
Lauramide DEA
Lauramide/Myristamide DEA
Lecithinamide DEA
Linoleamide DEA
Minkamide DEA
Myristamide DEA
Oleamide DEA
Olivamide DEA
Palm Kernelamide DEA
Palmamide DEA
Palmitamide DEA
Ricebranamide DEA
Ricinoleamide DEA
Sesamide DEA
Shea Butteramide/Castoramide DEA
Soyamide DEA
Stearamide DEA
Tallamide DEA

[1] Cosmetic Ingredient Review, Scientific Analyst/Writer, Washington, DC, USA
[2] Cosmetic Ingredient Review, Chemist, Washington, DC, USA
[3] Cosmetic Ingredient Review, Expert Panel Member, Washington, DC, USA
[4] Cosmetic Ingredient Review, Director, Washington, DC, USA

Corresponding Author:
Alan Andersen, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.
Email: cirinfo@cir-safety.org

Table 1. Conclusions of Previously Reviewed Ingredients and Components.

Ingredient	Conclusion	Reference
Previously Reviewed Ingredients		
Cocamide DEA	Safe as used in rinse-off products; safe at concentrations ≤10% in leave-on products; should not be used as an ingredient in cosmetic products in which N-nitroso compounds are formed	1
Isostearamide DEA	Safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 40%	3
Lauramide DEA	Safe as used; should not be used in products containing nitrosating agents	2
Linoleamide DEA	Safe as used; should not be used in products containing nitrosating agents	2
Myristamide DEA	Safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 40%	3
Oleamide DEA	Safe as used; should not be used in products containing nitrosating agents	2
Stearamide DEA	Safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 40%	3
Components		
DEA (likely an impurity)	Current tentative conclusion: DEA and its salts, except for DEA lauraminopropionate, are safe in the present practices of use and concentration when formulated to be non-irritating; these ingredients should not be used in cosmetic products in which N-nitroso compounds are formed; the available data are insufficient to conclude that DEA-Lauraminopropionate is safe under the intended conditions of use	28
Butyrospermum parkii (Shea) utter	Safe as used	42
Coconut acid	Safe as used	42
Corn acid	Safe as used	42
Elaeis guineensis (palm) Kernel oil	Safe as used	42
Elaeis guineensis (palm) oil		
Isostearic acid	Safe as used	43
Lanolin acid	Safe as used in topical applications	44
Lauric acid	Safe as used	45
Lecithin	Safe as used in rinse-off products; safe for use in leave-on products at concentrations of ≤15%; and the data were insufficient to determine the safety for use in products where lecithin is likely to be inhaled; should not be used in cosmetic products in which N-nitroso compounds may be formed	29
Mink oil	Safe as used	46
Myristic Acid	Safe as used	47
Olea europaea (live) fruit oil	Safe as used	42
Oleic Acid	Safe as used	45
Orbignya oleifera (babassu) oil	Safe as used	42
Palmitic acid	Safe as used	45
Persea gratissima (avocado) oil	Safe as used	42
Prunus amygdalus dulcis (sweet almond) oil	Safe as used	42
Prunus armeniaca (apricot) kernel oil	Safe as used	42
Rice Bran acid	Safe as used	42
Ricinoleic acid	Safe as used	31
Ricinus communis (castor) seed oil	Safe as used	31
Sesamum indicum (sesame) oil	Safe as used	42
Soy acid	Safe as used	42
Stearic acid	Safe as used	45
Tall oil acid	Safe as used	33
Tallow	Safe as used	48
Wheat germ acid	Safe as used	42
Zea mays (corn) oil	Safe as used	42

Abbreviation: DEA, diethanolamine.

Tallowamide DEA
Undecylenamide DEA
Wheat germamide DEA

The CIR Expert Panel has previously reviewed the related ingredients, lauramide DEA, linoleamide DEA, and oleamide DEA, and concluded that they are safe as used, but not in

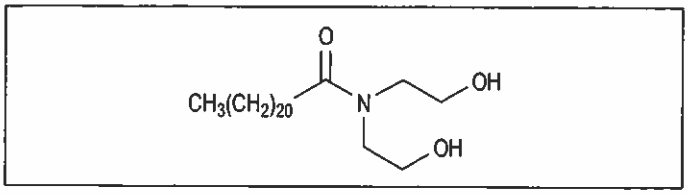


Figure 1. Behenamide diethylamine (DEA).

products containing nitrosating agents.[2] The Expert Panel also concluded in a previous review that isostearamide DEA, myristamide DEA, and stearamide DEA are safe for use in rinse-off products[3] and in leave-on products at concentrations that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 40%. Table 1 provides information on the components included in the review of DEA.

Chemistry

Definition and Structure

The diethanolamides consist of covalent, tertiary amides, whereby 2 of the nitrogen substituents are ethanol (or at least an ethanol residue) and the third is a carbonyl attached substituent. Figure 1 is an example of behenamide DEA, a tertiary amide wherein 2 of the nitrogen substituents are ethanol and the third is a 22 carbon, carbonyl-attached chain. Although these ingredients are not salts and do not readily dissociate in water, amidases, such as fatty acid amide hydrolase which is known to be present in human skin, could potentially convert these amides to DEA and the corresponding fatty acids.[4-6]

The CAS registry numbers, definitions, functions, and structures of cocamide DEA and the diethanolamides under consideration are presented in Table 2. The available chemical and physical properties for these ingredients are provided in Table 3.

Method of Manufacture

Although specific methods of manufacture for most of the ingredients included in this assessment were not available, in general these diethanolamides can be produced via condensation reaction with an acid. Cocamide DEA, for example, is produced by a condensation reaction at a 1:1 or 1:2 molar ratio of a mixture of methyl cocoate, coconut oil, whole coconut acids, or stripped coconut fatty acids to DEA.[2] Cocamide DEA has also been produced by the reaction of refined coconut oil with DEA in the presence of sodium methoxide (catalyst), yielding cocamide DEA, 10% glycerine, and 5% coconut fatty acid amide.[1] Lauramide DEA is produced by a condensation reaction at a 1:1 or 1:2 molar ratio of a mixture of lauric and myristic acid to DEA[2] and lauramide DEA is produced by the condensation of lauric acid methyl ester with DEA at elevated temperature and in the presence of a catalyst.[7] Oleamide DEA is produced by a condensation reaction at a 1:1 or 1:2 molar ratio of a mixture of oleic acid to DEA,[2] and linoleamide DEA is produced by a condensation reaction at a 1:1 or 1:2 molar ratio of a mixture of linoleic acid or its methyl ester to DEA.[2]

Impurities

The manufacturing process of a 1:2 mixture of fatty acid to DEA produces ethylene glycol and free DEA residues; however, the manufacture of a 1:1 mixture contains much less free amine. Alkanolamides are manufactured by base-catalyzed condensation of DEA, and the *methyl ester of long-chain fatty acids are susceptible to nitrosamine formation.*[2]

Cocamide DEA. Although manufacturing data available for various grades of cocamide DEA suggest free DEA at 4.0% to 8.5%,[1] a National Toxicology Program (NTP) study revealed cocamide DEA at approximately 18.2% free DEA by weight, alkanolamides of unsaturated acids, and amine salts of the acids, and *N*-Nitrosodiethanolamine (NDELA) detected at a concentration of 219 parts per billion (ppb).[8] In 9 commercial samples of cocamide DEA analyzed for DEA,[9] the amount of DEA ranged from 3.2% to 14.0%. The NDELA was not found in any of the samples.

Lauramide DEA. Various grades of lauramide DEA available for cosmetic use have a free amine value of 10 to 35.[2] Results of an NTP study show the purity of lauramide DEA was approximately 90% for lauric acid DEA condensate, with approximately 5% amine (probably DEA) and 5% other organic impurities.[7] The NDELA was detected at a concentration of 3600 ppb. The report also stated that, based on data provided by the manufacturer the lauramide DEA contained 0.83% free DEA by weight and approximately 9% other organic impurities. The DEA in 9 commercial samples of lauramide DEA ranged from 1.2% to 12.4%. The NDELA was not found.[9]

Stearamide DEA. Stearamide DEA is characterized by 9% to 12% free fatty acids (as oleic acid) and 2% to 6% free amines (as DEA).[3]

Oleamide DEA. Oleamide DEA contains 6.0% to 7.5% free fatty acids (as oleic acid).[2] In an NTP study, the oleic acid DEA condensate content was 47.5%.[10] Impurities were identified as other fatty acid alkanolamides (approximately 30%), other fatty acids, and unidentified impurities. Free DEA was estimated at 0.19%; NDELA was detected at a concentration of 68 ppb.

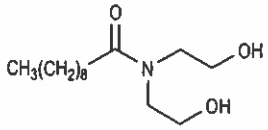
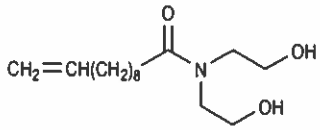
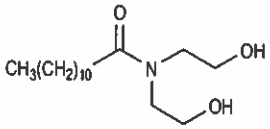
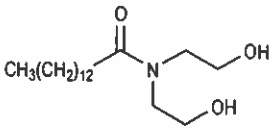
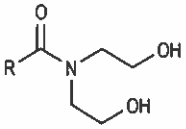
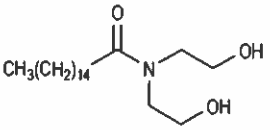
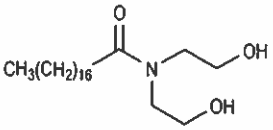
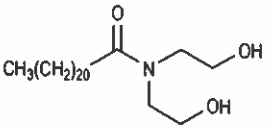
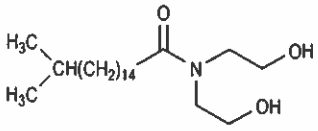
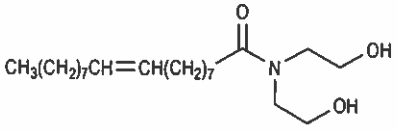
Linoleamide DEA. In the analysis of commercial sample of linoleamide DEA, DEA was detected at 4.3% to 5.0%.[9] The NDELA was not found in any of the samples.

Use

Cosmetic. Cocamide DEA is reported to function in cosmetics as a surfactant foam booster or a viscosity increasing agent.[11] Most of the other diethanolamides are reported to have these same functions, although a few are reported to function as a hair and conditioning agent, surfactant-cleansing or surfactant-emulsifying agent, or as an opacifying agent.

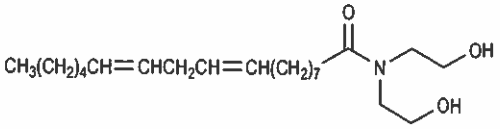
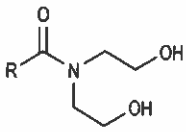
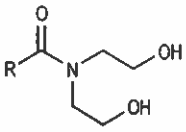
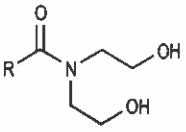
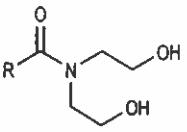
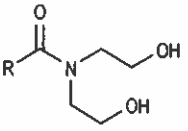
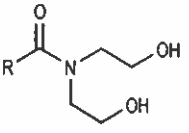
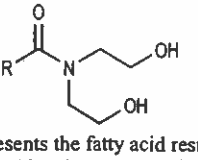
According to information supplied to the Food and Drug Administration by industry as part of the Voluntary Cosmetic Registration Program (VCRP), cocamide DEA is used in 710

Table 2. Definitions and Structures.

Ingredient CAS No.	Definition	Function(s)[11]	Formula/structure
Alkyl amides			
Capramide DEA 136-26-5	A mixture of ethanolamides of capric acid	Surf-Foam Boosters; Visc Incr Ag.-Aq	
Undecylenamide DEA 60239-68-125377-64-4	A mixture of ethanolamides of undecylenic acid	Hair Cond Ag; Surf - Foam Boosters; Visc Incr Ag-Aq	
Lauramide DEA 120-40-1	A mixture of ethanolamides of lauric acid	Surf-Foam Boosters	
Myristamide DEA 7545-23-5	A mixture of ethanolamides of myristic acid	Surf-Foam Boosters; Visc Incr Ag-Aq	
Lauramide/ Myristamide DEA	A mixture of ethanolamides of a blend of lauric and myristic acids	Surf.-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents a 12 or 14 carbon fatty acid residue
Palmitamide DEA 7545-24-6	a mixture of ethanolamides of palmitic acid.	Surf-Foam Boosters; Visc Incr Ag-Aq	
Stearamide DEA 93-82-3	A mixture of ethanolamides of stearic acid.	Surf-Foam Boosters; Visc Incr Ag-Aq	
Behenamide DEA 70496-39-8	A mixture of ethanolamides of behenic acid	Hair Cond Ag; Surf-Foam Boosters; Visc Incr Ag-Aq	
-Branched			
Isostearamide DEA 52794-79-3	A mixture of ethanolamides of isostearic acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 one example of an "iso"
-Partially unsaturated			
Oleamide DEA 5299-69-493-83-4	A mixture of ethanolamides of oleic acid	Surf-Foam Boosters; Visc Incr Ag-Aq	

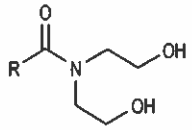
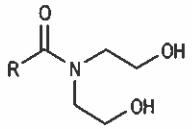
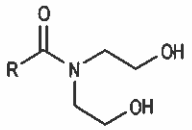
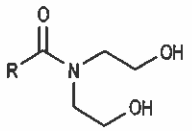
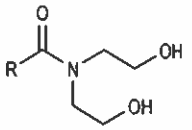
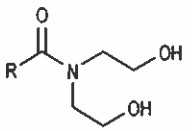
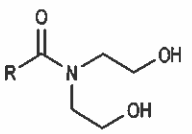
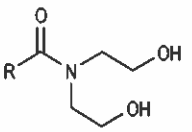
(continued)

Table 2. (continued)

Ingredient CAS No.	Definition	Function(s)[11]	Formula/structure
Linoleamide DEA 56863-02-6	A mixture of ethanolamides of linoleic acid	Hair Cond Ag; Surf-Foam Boosters; Visc Incr Ag-Aq.; Hair Cond Ag; Surf-Foam Boosters; Visc Incr Ag-Aq	
Natural source mixtures			
Almondamide DEA 124046-18-0	A mixture of ethanolamides of the fatty acids derived from almond oil	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from almond oil
Apricotamide DEA 185123-36-8	A mixture of ethanolamides of the fatty acids derived from Prunus Armeniaca (Apricot) Kernel Oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from *Prunus Armeniaca* (Apricot) Kernel Oil
Avocadamide DEA 124046-21-5	A mixture of ethanolamides of the fatty acids derived from Persea Gratissima (Avocado) Oil	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from *Persea Gratissima* (Avocado) Oil
Babassuamide DEA 124046-24-8	A mixture of ethanolamides of the fatty acids derived from Orbignya Oleifera (Babassu) Oil	Hair Cond Ag; Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from *Orbignya Oleifera* (Babassu) Oil
Cocamide DEA 61791-31-9	A mixture of ethanolamides of coconut acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from coconut acid
Cornamide DEA	A mixture of ethanolamides of corn acid	Surf. - Foam Boosters; Visc. Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from corn acid
Cornamide/Cocamide DEA	The diethanolamide of a mixture of coconut acid and the fatty acids obtained from Zea Mays (Corn) Oil	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from coconut acid and Zea Mays (Corn) Oil

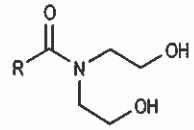
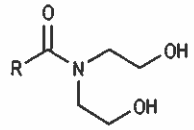
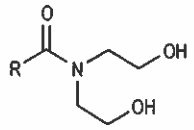
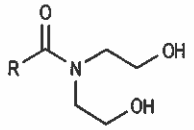
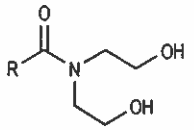
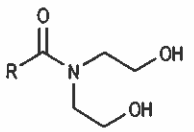
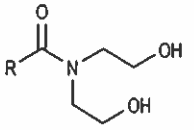
(continued)

Table 2. (continued)

Ingredient CAS No.	Definition	Function(s)[11]	Formula/structure
Hydrogenated Tallowamide DEA 68440-32-4	A mixture of ethanolamides of the fatty acids derived from hydrogenated tallow	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from hydrogenated tallow
Lanolinamide DEA [85408-88-4]	A mixture of ethanolamides of Lanolin Acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from lanolin acid
Lecithinamide DEA	The mixture of reaction products of DEA and the fatty acids of lecithin.	Hair Cond Ag; Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from lecithin
Minkamide DEA 124046-27-1	A mixture of ethanolamides of the fatty acids derived from mink oil.	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from mink oil
Olivamide DEA 124046-30-6	A mixture of ethanolamides of the fatty acids derived from olive oil	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from olive oil
Palm Kernelamide DEA 73807-15-5	A mixture of ethanolamides of the fatty acids derived from Elaeis Guineensis (Palm) Kernel Oil	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from *Elaeis Guineensis* (Palm) Kernel Oil
Palmamide DEA	A mixture of ethanolamides of the fatty acids derived from Elaeis Guineensis (Palm) Oil	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from *Elaeis Guineensis* (Palm) Oil
Ricebranamide DEA	A mixture of ethanolamides of rice bran acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from rice bran acid

(continued)

Table 2. (continued)

Ingredient CAS No.	Definition	Function(s)[11]	Formula/structure
Ricinoleamide DEA 40716-42-5	A mixture of ethanolamides of ricinoleic acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the ricinoleic acid residue
Sesamide DEA 124046-35-1	A mixture of diethanolamides of the fatty acids derived from Sesamum Indicum (Sesame) Oil	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from *Sesamum Indicum* (Sesame) Oil
Shea Butteramide/ Castoramide DEA	A mixture of diethanolamides of the fatty acids derived from Butyrospermum Parkii (Shea Butter) and Ricinus Communis (Castor) Seed Oil	Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from *Butyrospermum Parkii* (Shea Butter) and *Ricinus Communis* (Castor) Seed Oil
Soyamide DEA 68425-47-8	A mixture of ethanolamides of soy acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from soy acid
Tallamide DEA 68155-20-4	A mixture of ethanolamides of the fatty acids derived from tall oil acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from tall oil acid
Tallowamide DEA 68140-08-9	A mixture of ethanolamides of tallow acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from tallow acid
Wheat germamide DEA 124046-39-5	A mixture of diethanolamides of wheat germ acid	Surf-Foam Boosters; Visc Incr Ag-Aq	 wherein RC(O) represents the fatty acid residues derived from wheat germ acid

Abbreviations: Aq, aqueous; DEA, diethanolamine; Hair Cond Ag, hair conditionaing agent; Surf-Foam Boosters, surfactant foam boosters; Visc Incr Ag, viscosity increasing agents.

cosmetic formulations, the majority (596) of which are rinse-off formulations.[12] A use concentration survey conducted by the Personal Care Products Council (Council) showed cocamide DEA use at concentrations of 0.5% to 7%.[13,14] The highest concentration of cocamide DEA is reported to be used in leave-on products is 2%. Lauramide DEA is reported to be used in 281 cosmetic formulations at 0.2% to 9%; the use of lauramide DEA at 9% is the highest concentration of use in a leave-on product reported for any of the diethanolamides. Linoleamide DEA has the highest concentration of use

Table 3. Physical and Chemical Properties.

Property	Value	Reference
Cocamide DEA		
Physical form	Clear viscous liquid	1,8
Color	Amber or yellow	1,8
Odor	Faint coconut	1
Molecular weight	280-290	8
Melting point	23°C-35°C	1
Water solubility	Soluble in water	1
pH (10% aq. solution)	9.5-10.5	1
Acid value	3.0 max	1
Capramide DEA		
Molecular weight	259.39	49
Density (predicted)	1.001 ± 0.06 g/cm^3	49
Boiling point (predicted)	417.9°C ± 30.0°C	49
log P (predicted)	3.014 ± 0.270	49
Undecylenamide DEA		
Molecular weight	271.40	49
Density (predicted)	1.002 ± 0.06 g/cm^3	49
Boiling point (predicted)	440.4°C ± 40.0°C	49
Lauramide DEA		
Physical form	Viscous liquid or waxy solid	7
Color	Light yellow (liquid) or white to light yellow (solid)	2
Odor	faint, characteristic	2
Molecular weight	287.44	49
Density	0.984 ± 0.06 g/cm^3 (at 20°C)	49
Refractive index	1.4708 (n30/L)	2
Melting point	37°C-47°C	2
Boiling point	443.2°C ± 0.270°C	49
Water solubility	Dispersible	2
pH (10% aq dispersion)	9.8-10.8	2
Acid value	0.1-14	2
Alkaline value	6-200	2
log P (predicted)	4.033 ± 0.270 (at 25°C)	49
pK_a	14.13 (at 25°C)	49
pK_b	−0.85 (at 25°C)	
Myristamide DEA		
Physical form	Waxy solid	3
Color	White to off-white	3
Melting point	40°C-54°C	3
Water solubility	Dispersible	3
Other solubility	Soluble in alcohol, chlorinated hydrocarbons, and aromatic hydrocarbons; dispersible in mineral spirits, kerosene, white mineral oils, and natural fats and oils	3
pH (10% aq dispersion)	9.5-10.5	3
log P (predicted)	5.025 ± 0.270	49
Acid value	1 (max)	3
Alkaline value	26-50	3
Palmitamide DEA		
Molecular weight	343.54	49
Density (predicted)	0.959 ± 0.06 g/cm^3 (20°C)	49
Boiling point (predicted)	492.5 ± 30.0°C	49
log P (predicted)	6.071 ± 0.270	49
Stearamide DEA		
Physical form	Wax-like solid	3
Color	White to pale yellow	3
Molecular weight	371.60	49
Density (predicted)	0.959 ± 0.06 g/cm^3 (20°C)	49
pH (1% aq. dispersion)	9-10	3
log P (predicted)	7.090 ± 0.270	49
Behenamide DEA		
Molecular weight	427.70	49
Density (predicted)	0.935 ± 0.06 g/cm^3 (20°C)	49
Boiling point (predicted)	562.1°C ±30.0°C	49
log P (predicted)	9.128 ± 0.270	49
Oleamide DEA		
Physical form	Liquid	2
Color	Amber	2
Molecular weight	387.68	10
Specific gravity	0.99 (25/25°C)	2
Phase transition	congeals at −8°C	2
Boiling point (predicted)	525.6°C ± 45.0°C	49
Water solubility	Dispersible	2
Other solubility	Soluble in alcohols, glycols, ketones, esters, benzenes, chlorinated solvents, and aliphatic hydrocarbons	2
pH	9-10	2
log P (predicted)	6.681 ± 0.275	49
Linoleamide DEA		
Physical form	Syrup-like liquid or wax-like mass	2
Color	Light yellow (liquid) or white to yellow (mass)	2
Odor	Characteristic	2
Specific gravity	0.972-0.982 (25°/25°C)	2
Water solubility	Slightly soluble	2
Boiling point (predicted)	525.6°C ± 50.0°C	49
Other solubility	Soluble in ethanol, propylene glycol, and glycerin; insoluble in mineral oil	2
Acid value	2.0 (max)	2
Alkaline value	25-50 (calculated as DEA)	
log P (predicted)	6.277 ± 0.275	49
Ricinoleamide DEA		
Molecular weight	385.58	49
Density (predicted)	1.007± 0.06 g/cm^3 (20°C)	49
Boiling point (predicted)	560.5°C ± 50.0°C	49
log P (predicted)	4.867 ± 0.289	49

Abbreviations: aq, aqueous; DEA, diethanolamine; max, maximum.

reported, 12% in rinse-off formulations. The remaining diethanolamides have less than 35 reported uses. Concentration and frequency of use data for in-use diethanolamides are provided in Table 4. Ingredients not reported to be in use, according to VCRP data and the Council survey, are listed in Table 5.

Cocamide and lauramide DEA are reported to be used in baby products, and some of the dialkanolamides are used in products that come in contact with the mucous membranes.

Table 4. Frequency and Concentration of Use According to Duration and Type of Exposure.[a]

	Capramide DEA		Cocamide DEA		Isostearamide DEA	
	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]
Totals[b]	1	NR	710	0.5-7	2	NR
Duration of Use						
Leave-on	*NR*	*NR*	*37*	*0.5-2*	*2*	*NR*
Rinse off	*1*	*NR*	*596*	*1-7*	*NR*	*NR*
Diluted for (Bath) use	*NR*	*NR*	*77*	*0.4-6*	*NR*	*NR*
Exposure Type						
Eye area	NR	NR	2	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-sprays	NR	NR	1	NR	NR	NR
Incidental inhalation-powders	NR	NR	NR	NR	NR	NR
Dermal contact	NR	NR	342	0.5-6	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair-non-coloring	1	NR	221	1-7	NR	NR
Hair-coloring	NR	NR	147	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	274	0.4-6	NR	NR
Baby products	NR	NR	10	2	NR	NR

	Lauramide DEA		Lauramide/Myristamide DEA		Linoleamide DEA	
	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]
Totals[b]	281	0.2-9	1	NR	32	1-12
Duration of use						
Leave-on	*21*	*0.2-9*	*NR*	*NR*	*3*	*NR*
Rinse-off	*232*	*0.2-8*	*1*	*NR*	*19*	*1-12*
Diluted for (Bath) use	*28*	*2-8*	*NR*	*NR*	*10*	*3*
Exposure type						
Eye area	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-sprays	13	0.2-9	NR	NR	1	NR
Incidental inhalation-powders	NR	NR	NR	NR	NR	NR
Dermal contact	165	0.2-9	1	NR	20	1-7
Deodorant (underarm)	1 [a]	2	NR	NR	NR	NR
Hair-noncoloring	115	0.3-8	NR	NR	4	3-7
Hair-coloring	2	0.2	NR	NR	7	7-12
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	139	2-8	NR	NR	17	3-7
Baby products	1	NR	NR	NR	NR	NR

	Myristamide DEA		Oleamide DEA		Palm Kernelamide DEA	
	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]
Totals[b]	NR	0.8	5	5	4	2
Durotion of use						
Leave-on	*NR*	*NR*	*3*	*NR*	*NR*	*NR*
Rinse off	*NR*	*0.8*	*2*	*5*	*4*	*2*
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-sprays	NR	NR	NR	NR	NR	NR
Incidental inhalation-powders	NR	NR	NR	NR	NR	NR
Dermal contact	NR	0.8	4	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR

(continued)

Table 4. (continued)

	Myristamide DEA		Oleamide DEA		Palm Kernelamide DEA	
	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]
Hair-noncoloring	NR	NR	1	NR	4	2
Hair-coloring	NR	NR	NR	5	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	0.8	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR

	Soyamide DEA		Stearamide DEA	
	# of Uses[12]	Conc of Use (%)[13]	# of Uses[12]	Conc of Use (%)[13]
Totals[b]	1	NR	10	0.5
Durotion of use				
Leave-on	*NR*	*NR*	*9*	*NR*
Rinse-off	*1*	*NR*	*1*	*0.5*
Diluted for (Bath) use	*NR*	*NR*	*NR*	*NR*
Exposure type				
Eye area	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	NR	NR	NR
Incidental inhalation-powders	NR	NR	NR	NR
Dermal contact	NR	NR	9	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair-noncoloring	1	NR	1	0.5
Hair-coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR
Baby products	NR	NR	NR	NR

Abbreviations: DEA, diethanolamine; NR, none reported.
[a] It is not known whether or not the product is a spray.
[b] Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses.

Table 5. Ingredients not Reported to be in Use.

Almondamide DEA
Apricotamide DEA
Avocadamide DEA
Babassuamide DEA
Behenamide DEA
Cornamide DEA
Cornamide/cocamide DEA
Hydrogenated tallowamide DEA
Lactamide DEA
Lanolinamide DEA
Lecithinamide DEA
Minkamide DEA
Olivamide DEA
Palmamide DEA
Palmitamide DEA
Ricebranamide DEA
Ricinoleamide DEA
Sesamide DEA
Shea butteramide/castoramide DEA
Tallamide DEA
Tallowamide DEA
Undecylenamide DEA
Wheat germamide DEA

Abbreviation: DEA, diethanolamine.

Additionally, some of the dialkanolamides are reported to be present in hair sprays or fragrance formulations. In practice, 95% to 99% of the aerosols released from cosmetic sprays have aerodynamic equivalent diameters in the range of 10 to 110 μm.[15,16] Therefore, most aerosols incidentally inhaled from these sprays are deposited in the nasopharyngeal region and are not respirable.[17,18] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic diameters in the range considered to be respirable.[18] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays compared to other cosmetic sprays.

Fatty acid dialkanolamides are listed in Annex III of the European Cosmetics Directive, which is a list of substances cosmetic products must not contain except when subject to restrictions,[19] which state a maximum secondary amine content of 0.5% in the finished product; these amides are not use with nitrosating systems; maximum secondary amine content of 5% for raw materials; maximum nitrosamine content of 50 μg/kg; and that these substances are kept in nitrite-free containers. The ingredients listed in Annex III with these restrictions, as well as additional EC information,[20] are provided in Table 6.

Table 6. Status for use in Europe According to the EC Cosing Database.

Fatty Acid Dialkanolamides—Listed in Annex III—Restrictions[19] (Maximum secondary amine content of 0.5% in the finished product; do not use with nitrosating systems; maximum secondary amine content of 5% for raw materials; maximum nitrosamine content of 50 µg/kg; keep in nitrite free containers)
Almondamide DEA
Apricotamide DEA
Avocadamide DEA
Babassuamide DEA
Behenamide DEA
Capramide DEA
Cocamide DEA
Cornamide DEA
Cornamide/Cocamide DEA
Hydrogenated Tallowamide DEA
Isostearamide DEA
Lanolinamide DEA
Lauramide DEA
Lauramide/Myristamide DEA
Lecithinamide DEA
Linoleamide DEA
Minkamide DEA
Myristamide DEA
Oleamide DEA
Olivamide DEA
Palm Kernelamide DEA
Palmamide DEA
Palmitamide DEA
Ricebranamide DEA
Ricinoleamide DEA
Sesamide DEA
Soyamide DEA
Stearamide DEA
Tallamide DEA
Tallowamide DEA
Undecylenamide DEA
Wheat Germamide DEA
Listed in EC Inventory—no annex specified[20]
Shea Butteramide/Castoramide DEA

Abbreviation: DEA, diethanolamine.

Noncosmetic

Many of the diethanolamides included in this safety assessment are used as indirect food additives.[21] Cocamide, soyamide, and tallamide DEA are used in manufacturing as surface active agents.[22] Cocamide DEA is used as a corrosion inhibitor in metalworking fluids and in polishing agents.[1]

Toxicokinetics

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Lauramide DEA. Human liver slices and liver slices from diethylhexyl phthalate (DEHP)-induced and untreated male F344 rats were incubated with [^{14}C]lauramide DEA.[23] Lauramide DEA "partitioned well" into the human liver slices and the liver slices from DEHP-induced and untreated rats. Approximately 70% of the radioactivity absorbed into the slices in 4 hours. The absorbed radioactivity was present mostly as lauramide DEA. In the media from the human, rat, and DEHP-induced rat liver slice incubations, 32%, 18%, and 43% of the radioactivity, respectively, was present in the form of metabolites. The analytes present in the incubation media included half-acid amides, parent lauramide DEA, and 3 other metabolites that are products of ω- and ω-1 to 4 hydroxylation.

The in vitro metabolism of [^{14}C]lauramide DEA, randomly labeled on the DEA moiety, was examined in liver and kidney microsomes from rats and humans to determine the extent of hydroxylation and to determine the products formed.[24] Incubation of lauramide DEA with liver microsomes from control and DEHP-treated rats produced 2 major high performance liquid chromatography peaks that were identified as 11-hydroxy- and 12-hydroxy-lauramide DEA. Treatment with DEHP increased the 12-hydroxylation rate 5-fold, while the 11-hydroxylase activity was unchanged. Upon comparison of lauramide DEA hydroxylation rates using human liver microsomes with the rates measured using rat liver and kidney microsomes, the lauramide DEA 12-hydroxylase activity in human liver microsomes was similar to the activity in liver microsomes from control rats. The 12-hydroxylase activity in liver microsomes was 3 times greater than that observed in rat kidney microsomes.

Dermal

Non-Human

Lauramide DEA. Groups of 4 male B6C3F$_1$ mice and 4 F344 rats were dosed dermally with [^{14}C]lauramide DEA that was randomly labeled on the DEA moiety.[23] The vehicle was ethanol. A nonocclusive application was made to a 0.5 in^2. area of mouse skin and to a 1 in^2. area of rat skin. At the end of the study, the excised skin was rinsed with ethanol. Absorption was calculated from the total disposition of radioactivity in the tissues, urine, feces, and dose site. In mice dosed with 5 to 800 mg/kg [^{14}C]lauramide DEA, 50% to 70% of the applied radioactivity was absorbed at 72 hours, and absorption was similar for all the doses. Approximately 32% to 55% of the radioactivity was excreted in the urine. In rats dosed with 25 or 400 mg/kg lauramide DEA, 21 % to 26% of the radioactivity penetrated the skin in 72 hours, and 3% to 5% was recovered at the application site. Approximately 20% to 24% of the radioactivity was recovered in the urine. The tissue/blood ratio was greatest in the liver and kidney. Lauramide DEA and the half-acid amide metabolites were detected in the plasma, with maximum levels found 24 hours after dosing.

The researchers also examined the effects of repeated administration lauramide DEA on absorption and excretion. Lauramide DEA, 25 mg/kg/d, was applied to 5 rats, 5 times/wk, for 3 weeks. The rate of absorption of lauramide DEA did not vary much at the different collection time points, and the amounts excreted were similar at each collection period.

Oral

Non-Human

Lauramide DEA. Three male F344 rats were dosed orally with [^{14}C]lauramide DEA that was randomly labeled on the DEA moiety, 16 to 18 μCi/dose, and that was formulated with an appropriate amount of unlabeled lauramide DEA and water to give delivery of the target dose in a volume of 5 mL/kg body weight (bw).[23] After oral dosing with 1000 mg/kg [^{14}C]lauramide DEA, approximately 10%, 60%, and 79% of the dose was recovered in the urine after 6, 24, and 72 hours, respectively. Approximately 4% of the dose was recovered in the tissues after 72 hours, with almost 3% found in adipose tissue and 1.3% in the liver. At 6 hours, no DEA, DEA metabolites, or unchanged lauramide DEA were present in the urine; only very polar metabolites were found. The researchers postulated that the metabolites were carboxylic acids, and that the acid function was formed from the lauryl chain.

Intravenous

Non-Human

Lauramide DEA. In all, 3 male B6C3F$_1$ mice and 4 F344 rats were dosed intravenously (iv) with [^{14}C]lauramide DEA that was randomly labeled on the DEA moiety, 3 to 5 μCi and 16 to 17 μCi, respectively, and that was formulated to deliver a target dose in a volume of 4 mL/kg in mice and 1 mL/kg in rats.[23] The dose for mice was 50 mg/kg, and the dose for rats was 25 mg/kg. In B6C3F$_1$ mice, lauramide DEA was quickly metabolized and eliminated. At 24 hours after dosing, approximately 95% of the dose was excreted, with 90% found in the urine; the highest concentrations and total amounts of the lauramide DEA were in adipose tissue. In F344 rats, 50% of the dose was excreted in the urine within the first 6 hours, and more than 80% was excreted in the urine by 24 hours. The rats were killed at 72 hours after dosing, and only 3% of the dose was recovered in the tissues; 1% of the dose was in the adipose tissue and 0.67% was found in the liver.

Toxicological Studies

Single-Dose (Acute) Toxicity

Dermal

Cocamide DEA. The acute dermal toxicity of cocamide DEA was evaluated using 3 male and 3 female albino rabbits.[22,25] Cocamide DEA 2 g/kg were applied to intact and abraded skin for 24 hours using occlusive patches. None of the animals died, and the lethal dose, 50% (LD_{50}) was >2 g/kg.

Lauramide DEA. In an acute dermal toxicity study using guinea pigs, 50% lauramide DEA in corn oil was nontoxic.[2] In a study to evaluate the acute dermal toxicity of lauramide DEA in 3 male and 3 female albino rabbits,[22,25] 2 g/kg lauramide DEA were applied to intact and abraded skin for 24 hours using occlusive patches. None of the animals died, and the LD_{50} was >2 g/kg.

Linoleamide DEA. Linoleamide DEA, tested as 10% aqueous (aq) and undiluted, was nontoxic in acute studies with guinea pigs.[2]

Oral

Cocamide DEA. In an acute oral toxicity test in male and female Sprague-Dawley rats, undiluted cocamide DEA had an LD_{50} of 12.2 g/kg.[2] In an acute oral toxicity study of cocamide DEA using groups of 3 male and 3 female Wistar rats, 3 or more animals per group died with doses of ≥6.3 g/kg.[26] The LD_{50} of cocamide DEA in several other studies using rats was >5 g/kg or 5 mL/kg, which was the highest dose tested.[22,25]

Lauramide DEA. In rats, the oral LD_{50} of 25% lauramide DEA in corn oil was >5 g/kg, of 10% aq was 2.7 g/kg, of a shampoo formulation containing 8% lauramide DEA was 9.63 g/kg, and of a bubble bath containing 6% lauramide DEA was >15 g/kg.[2] The acute oral toxicity of lauramide DEA, 70% pure (composition included 25% water and 5% DEA), was evaluated using groups of 5 male and 5 female Wistar rats.[25] The animals were gavaged with a single aq dose of 5.0 g/kg bw; 1 male and 2 females rats died by day 4. The LD_{50} was >3.5 g/kg active ingredients. (The LD_{50} of the 70% solution was 0.5 g/kg). In another study using male and female Wistar rats, the oral LD_{50} of lauramide DEA, purity not specified, was > 5 mL/kg, which was the highest dose tested.[25]

Stearamide DEA. The oral LD_{50} of a mixture containing 35% to 40% stearamide DEA was >20 g/kg in CFW mice.[3]

Oleamide DEA. In rats, the oral LD_{50} of undiluted oleamide DEA was 12.4 mL/kg.[2]

Linoleamide DEA. In rats, the oral LD_{50} of undiluted and 10% aq linoleamide DEA was >5 g/kg, and the LD_{50} of a product containing 1.5% linoleamide DEA was 3.16 g/kg.[2]

Inhalation

Tallamide DEA. In an inhalation study, groups of 4 male Swiss-Webster mice were exposed to 86 to 219 mg/m^3 tallamide DEA for 3 hours.[22,25] Tallamide DEA produced sensory and pulmonary irritation at low concentrations. The lethal concentration, 50% (LC_{50}) value was >219 mg/m^3 (additional details were not provided).

Repeated Dose Toxicity

Dermal

Cocomide DEA. Eight New Zealand White (NZW) rabbits received 1.92% cocamide DEA on the intact or abraded skin of the back. Applications of 500 mg/kg of the test product were made 5×/wk for 4 weeks. Dermal irritation was observed at both intact and abraded application sites. No systemic effects attributed to dosing were observed.[2]

The repeated dose dermal toxicity of cocamide DEA (containing 18.2% free DEA by weight) was evaluated using mice and rats. Groups of 10 male and 10 female B6C3F$_1$ mice were dosed with 50, 100, 200, 400, or 800 mg/kg bw cocamide DEA

in ethanol (20-320 mg/mL), 5 exposures/wk, for 14 weeks.[8] Dermal irritation was observed at the application sites of males and females of the 800 mg/kg dose group. Epidermal and sebaceous gland hyperplasia, parakeratosis, chronic active inflammation, and ulceration were observed; severity generally increased with increased dose. Final mean bws and mean bw gains were similar for test and control animals. The absolute liver and kidney weights and relative liver and kidney weights to bws of males and females of the 800 mg/kg group, relative liver weights to bws of females of the 400 mg/kg group, and absolute lung weights and relative lung weights to bws of females of the 800 mg/kg group were significantly greater than that for those of the controls. The epididymal spermatozoal concentration was significantly greater in males of the 800 mg/kg dose group.

Groups of 20 male and 20 female F344/N rats were dosed dermally with 25, 50, 100, 200, or 400 mg/kg/bw cocamide DEA in ethanol (30-485 mg/mL), at 5 exposures/wk, for 14 weeks; 10 rats per group were used for clinical chemistry and hematology evaluation.[8] Vehicle only was applied to the negative control group. All animals survived until study termination. Dermal irritation was observed at the application sites of 2 males and 1 female of the 100 mg/kg group and in nearly all males and females of the 200 and 400 mg/kg dose groups. Lesions included epidermal and sebaceous gland hyperplasia, parakeratosis, chronic active inflammation, and ulceration; incidence and severity generally increased with increasing dose. Final mean bws and mean bw gains of males and females of the 200 and 400 mg groups were significantly less than those of the controls. Kidney weights of females of the 50 mg/kg group were significantly greater than those of the controls. Decreases in epididymal weights in 200 and 400 mg/kg males were attributed to decreased bws. Changes in some hematology and clinical chemistry parameters were noted, and the researchers stated there was an indication of altered lipid metabolism, as evidenced by decreased cholesterol and triglyceride concentrations. The incidences of renal tubule regeneration were greater in females of the 100 dose group, and the incidences and severities were greater in females of the 200 and 400 mg/kg dose groups, when compared to controls.

Lauramide DEA. The dermal toxicity of lauramide DEA was evaluated in two 13-week studies using Sprague-Dawley rats. No systemic toxic effects were observed for a 0.45% aq solution containing 4.0% lauramide DEA, tested in 15 females, and a solution containing 5.0% lauramide DEA, tested in 10 males and 10 females.[2]

Groups of 10 male and 10 female B6C3F$_1$ mice were dosed with 50, 100, 200, 400, or 800 mg/kg bw lauramide DEA in ethanol (90% purity; 0.83% free DEA by weight), 5 exposures/wk, for 14 weeks.[7] All animals survived until study termination. Dermal irritation was observed at the application sites of males and females dosed with 400 or 800 mg/kg lauramide DEA. Final mean bws and mean bw gains were similar for test and control animals. The absolute kidney weights of males of the 100, 400, and 800 mg/kg bw groups, the relative kidney to bws of all dosed males, and the liver weights of females of the 200, 400, and 800 mg/kg bw groups, were statistically significantly greater than those of the control mice. The absolute thymus weights of males of the 400 and 800 mg/kg groups were significantly less than those of the controls. There were no statistically significant differences in reproductive tissue evaluation or estrous cycle between the treated and the control groups. At the application site, incidences of nonneoplastic lesions of the skin, including hyperplasia of the epidermis and sebaceous gland, chronic inflammation, parakeratosis, and ulceration, were increased in males and females dosed with ≥200 mg/kg lauramide DEA.

Groups of 20 male and 20 female F344/N rats were dosed dermally with 25, 50, 100, 200, or 400 mg/kg bw lauramide DEA in ethanol, 5 exposures/wk for 14 weeks; 10 rats per group were used for clinical pathology.[7] All animals survived until study termination. Dermal irritation was observed at the application site of males dosed with ≥100 mg/kg and in females dosed with 200 or 400 mg/kg lauramide DEA. Final mean bws and mean bw gains of males of the 200 and 400 mg/kg bw group were statistically significantly less than those of the control group. Kidney weights of females dosed with 200 or 400 mg/kg bw were statistically significantly greater, and absolute liver weights of males dosed 400 mg/kg lauramide DEA were statistically significantly less, than those of the control groups. There were no statistically significant differences in reproductive tissue evaluation or estrous cycle between the treated and the control groups. At the application site, incidences of nonneoplastic lesions of the skin, including hyperplasia of the epidermis and sebaceous gland, chronic inflammation, parakeratosis, and ulceration, were statistically significantly increased with increasing dose.

Oleamide DEA. The repeated dose dermal toxicity of oleamide DEA (47.5% oleic acid DEA condensate content; 0.19% free DEA) was evaluated using mice and rats. Groups of 10 male and 10 female B6C3F$_1$ mice were dosed with 50, 100, 200, 400, or 800 mg/kg bw oleamide DEA in ethanol (20-320 mg/mL), 5 exposures/wk, for 13 weeks.[10] All animals, except 1 high dose male, survived until study termination. Final mean bws and bw gains of males of the 800 mg/kg group and females of the 400 mg/kg group were statistically significantly less than those of controls. Dermal irritation was observed at the application site of all treated males and for most females dosed with ≥100 mg/kg oleamide DEA. Lesions included epidermal hyperplasia, parakeratosis, suppurative epidermal and chronic active dermal inflammation, sebaceous gland hypertrophy, and ulceration; severity generally increased with increased dose. Heart weights of females of the 200 mg/kg and males and females of the 400 and 800 mg/kg groups, kidney weights of males of the 50, 100, and 400 mg/kg groups, and liver weights of all dose groups were statistically significantly greater than those of controls. The incidences of hematopoietic cell proliferation of the spleen of males of the 800 mg/kg group and females of the 400 and 800 mg/kg groups were statistically significantly greater than the controls. Sperm motility and

vaginal cytology parameters of dosed mice were similar to those of the controls.

Groups of 20 male and 20 female F344/N rats were dosed dermally with 25, 50, 100, 200, or 400 mg/kg bw oleamide DEA in ethanol (30-485 mg/mL), 5 exposures/wk for 13 weeks; 10 rats per group were used for clinical chemistry and hematology evaluation.[10] All animals survived until study termination. Dermal irritation was observed at the application site of most males dosed with ≥100 mg/kg and all females dosed with ≥50 mg/kg oleamide DEA. Lesions included epidermal hyperplasia, parakeratosis, suppurative epidermal and chronic active dermal inflammation, and sebaceous gland hypertrophy; severity generally increased with increased dose. The final mean bws and mean bw gains of males of the 200 and 400 mg/kg groups and mean bw gains of females of the 400 mg/kg group were statistically significantly less than controls; some associated lower organ weights were observed. Kidney weights were statistically significantly greater for females of the 200 and 400 mg/kg groups when compared to controls. Some increases in segmented neutrophil counts and alkaline phosphatase concentrations were reported. There were no biologically significant differences in sperm motility or vaginal cytology parameters between treated and control rats.

Linoleamide DEA. In a 13-week study using a formulation containing 3.0% linoleamide DEA, solutions were applied at 2.5%, 25% solution, or at a 25% solution that was rinsed after 15 minutes, to groups of 10 male and 10 female Sprague-Dawley rats. Dermal irritation was observed, and the formulation containing 3% linoleamide DEA was not a cumulative systemic toxicant.[2]

Oral

Lauramide DEA. In the first of two 13-week dietary studies, groups of 15 male and 15 female SPF rats were fed 0% to 2% lauramide DEA. A reduction in growth was associated with reduced feed intake at doses of ≥0.5% lauramide DEA. There were no treatment-related gross or microscopic lesions. The no-effect dose was 0.1% lauramide DEA. In the second study, groups of 20 male and 20 female Wistar rats were fed 0 to 250 mg/kg/d. No adverse effects were reported, and the no-effect dose for rats was 250 mg/kg/d. Groups of 4 male and 5 female Beagle dogs were fed 0 to 5000 parts per million (ppm) lauramide DEA for 12 weeks. No adverse effects were reported, and the no-effect dose for dogs was 5000 ppm lauramide DEA.[2]

Reproductive and Developmental Toxicity

Cocamide DEA

Groups of gravid female Sprague-Dawley rats (number per group not specified) were gavaged with 5 mL/kg bw of 0, 100, 300, or 1000 mg/kg/d cocamide DEA, 90% to 95% pure, on days 6 to 15 of gestation.[25] Controls were dosed with arachis oil. The dams were killed on day 20 of gestation. No deaths occurred in any of the groups. Salivation and propulsion of the head was observed in all test groups; salivation was "severe" in the 1000 mg/kg group. The bws and weight gains were comparable for all groups, as were fetal bws. Postimplantation loss and total embryonic deaths were statistically significantly increased in all treated groups compared to the controls; these findings were considered incidental by the researcher because 1 single female accounted for these findings in each group. Although retardation of ossification was statistically significantly increased in the 300 and 1000 mg/kg groups, these values were within the normal range of variation for this strain. The incidence of ossification of the skull bones was statistically significantly increased in 2 dams (accounting for 10 of the 17 findings) in the 1000 mg/kg group. The NOAELs for maternal toxicity and developmental toxicity were both reported as 1000 mg/kg/d.

No other reproductive and developmental toxicity studies of the diethanolamides were found. Because DEA may be an impurity in the diethanolamides, and amidases in the skin might convert some of the diethanolamide to DEA and the corresponding fatty acid, data on DEA and other dialkanolamide components was reviewed.

Diethanolamine. Hair dyes containing up to 2% DEA were applied topically to the shaved skin of groups of 20 gravid rats on days, 1, 4, 7, 10, 13, 16, and 19 of gestation, and the rats were killed on day 20 of gestation. No developmental or reproductive effects were observed.[27]

Gravid mice dosed dermally with 20 to 320 mg/kg DEA from day 6 of gestation through PND 21 showed no effects on skeletal formation, but dose-dependent effects on some growth and developmental parameters were observed. In a study in which parental mice were treated dermally with 20 to 320 mg/kg DEA for 4 weeks prior to mating, sperm motility was decreased in a dose-dependent manner. In rats and rabbits, dermal dosing with up to 1500 mg/kg/d and 350 mg/kg/d DEA, respectively, during gestation, did not have any fetotoxic or teratogenic effects. The NOEL for embryonal/fetal toxicity was 380 mg/kg/d for rats and 350 mg/kg/d for rabbits.[28]

In an oral developmental study in which rats were dosed with up to 1200 mg/kg/d DEA on days 6 to 15 of gestation, maternal mortality was observed at doses of ≥50 mg/kg; the NOEL for embryonal/fetal toxicity was 200 mg/kg/d. In a study in which gravid rats were dosed orally with up to 300 mg/kg/d DEA, the dams of the 300 mg/kg group were killed due to excessive toxicity; the LD_{50} was calculated to be 218 mg/kg. The LOAEL for both maternal toxicity and teratogenicity was 125 mg/kg/d.[28]

In a developmental study in which rats were exposed by inhalation to DEA on days 6 to 15 of gestation, the NOAEC for both maternal and developmental toxicity was 0.05 mg/L, and the NOAEC for teratogenicity was >0.2 mg/L.[28]

Lecithin. In oral studies, ≤1600 mg/kg lecithin was not a reproductive toxicant in mice or rats and ≤47 mg/kg was not a reproductive toxicant in rabbits. In an iv reproductive study, the lowest toxic daily iv dose for rats was >1000 mg/kg.

Lecithin, ≤3.0 mmol/L, had no significant effect on human sperm motility.[29]

Palm Oil. Crude palm oil (10%) was not a reproductive toxicant in a study in which male and female Wistar/NIN inbred weanling rats were fed prior to mating. Mean litter sizes were comparable between test and control groups. No significant changes were found in liver or kidney weight in adult animals. Neither untreated palm oil (15%) nor 15% heated palm oil in the diet induced anomalies with respect to fertility and in utero growth when fed to male and female Sprague-Dawley SPF rats prior to mating. In a study investigating the effects of palm oil on sexual maturation and endocrine function, vaginal opening was observed significantly earlier (compared to 5% corn oil control) in weanling rats fed 20% palm oil in the diet. No significant differences were observed in endocrine function.[30]

Palm Kernel Oil. Offspring from the mated adult Mongolian gerbils fed a diet containing 8.75% w/w palm kernel oil showed no statistically significant differences in frequency of litters, mean litter size, total of newborns, and suckling death. Animals receiving a basal diet served as the control.[30]

Ricinus Communis (Castor) Seed Oil. Groups of mice and rats fed diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10% castor oil continuously for 13 weeks had a slight decrease in epididymal weight (6% to 7%) in mid- and high-dose groups of male rats; however, this finding was not dose related. No effects on any other male reproductive end point (testes weight and epididymal sperm motility, density, or testicular spermatid head count) or female reproductive end point (estrous cycle length, or time spent in each phase of the cycle) were noted. Castor oil served as the vehicle control in a study evaluating the effect of long-term treatment with ICI 182,780 (an antiestrogen) on the rat testis. In the control group, 4 male Sprague-Dawley rats were injected subcutaneously (sc) with castor oil (0.2 mL) once per week and then killed 100 days after the first injection. Spermatogenesis appeared normal in each of the 4 control rats.[31]

Sesamum Indicum (Sesame) Seed Oil. Although not teratogenic, oral dosing with sesame oil (4 mL doses) increased the incidence of resorptions in rats when compared to controls. In a 42-week, 2-generation reproduction study involving rats, sesame oil (vehicle control, dose volume not stated) did not induce any adverse effects on reproductive performance, fertility, or reproductive organ weights of male or female rats through 2 consecutive generations. Oral dosing with sesame oil (vehicle control, single intragastric dose [not stated]) on day 9 of gestation also had no adverse effect on the fetal survival rate or crown-rump length in mice. Dosing with sesame oil sc did not adversely affect the development of mice receiving doses (0.05 mL injections) beginning at 3 to 5 days of age or induce teratogenic effects in their offspring. In a study involving rats, dosing with sesame oil sc (0.05 mL injections) did not have an adverse effect on the following when compared to untreated controls: uterine and ovarian weight (female rats) and weight of the testes, prostate, and seminal vesicles (male rats). Dosing with sesame oil intraperitoneally (0.4 mL) was associated with a marked increase in the incidence of deciduomas in mice.[32]

Tall Oil Acid. No treatment-related effects were observed in rats fed diets containing 5% and 10% tall oil acid in a 2-generation study.[33]

Genotoxicity

Cocamide DEA

Cocamide DEA was not mutagenic in an Ames assay (0.1-200 µg/plate), did not induce mutations in L5178Y mouse lymphoma cells (1.25-50 nL/mL), nor SCEs (0.5-30 µg/mL) or chromosomal aberrations (16-50 µg/mL) in Chinese hamster ovary (CHO) cells; all tests were performed with and without metabolic activation.[8] Significant increases in the frequencies of micronucleated normochromatic erythrocytes were found in peripheral blood of male and female mice at the end of a 14-week repeated dose study (described earlier).

Lauramide DEA

Lauramide DEA was not mutagenic or genotoxic in multiple Ames assays, a DNA damage assay using *Bacillus subtilis*, an in vitro transformation assay using Syrian golden hamster embryo cells, or an in vivo transformation assay using hamster embryo cells. Lauramide DEA was mutagenic in the spot test with 2 strains of *Salmonella typhimurium* (quantitative results were not provided).[2]

Lauramide DEA (0.3-1000 µg/plate) was not mutagenic in the Ames test with or without metabolic activation, was negative in a L5178Y mouse lymphoma assay (2.5-60 µg/mL), did not increase the number of chromosomal aberrations in CHO cells (1.5-100 µg/mL), with or without metabolic activation, and was not clastogenic in a mouse micronucleus test (50-800 mg/kg).[7] Lauramide DEA (2.49-49.7 µg/mL) induced SCEs in CHO cells, in the presence and the absence of metabolic activation.

Oleamide DEA

Oleamide DEA was not mutagenic in an Ames test (0.1-200 µg/plate) and did not induce mutations in L5178Y mouse lymphoma cells (1.25-20 nL/mL), with or without metabolic activation.[10]

Carcinogenicity

Dermal

Conclusions of NTP dermal carcinogenicity studies on lauramide DEA, oleamide DEA, cocamide DEA and DEA are summarized in Table 7.

Cocamide DEA

The carcinogenic potential of dermally applied cocamide DEA (containing 18.2% free DEA by weight) was assayed by the

Table 7. Conclusions of NTP Dermal Carcinogenicity Studies.

	Cocamide DEA[8]	Lauramide DEA[7]
Amount of free DEA	18.2%	0.83%
$B6C3F_1$ mice	0, 100, or 200 mg/kg	0, 100, or 200 mg/kg
Males	*Clear evidence of carcinogenic activity*	*No evidence of carcinogenic activity*
Basis	Increased incidences of hepatic and renal tubule neoplasms	
Females	*Clear evidence of carcinogenic activity*	*Some evidence of carcinogenic activity*
Basis	Increased incidences of hepatic neoplasms	Increased incidences of hepatocellular neoplasms
F344/N rats	0, 50, or 100 mg/kg	0, 50, or 100 mg/kg
Males	*No evidence of corcinogenic activity*	*No evidence of carcinogenic activity*
Basis		
Females	*Equivocal evidence of corcinogenic activity*	*No evidence of carcinogenic activity*
Basis	Marginal increase in the incidences of renal tubule neoplasms	
	Oleamide DEA[10]	Diethanolamine[50]
Amount of free DEA	0.19%	>99% pure
$B6C3F_1$ mice	0, 15, or 30 mg/kg	0, 40, 80, and 160 mg/kg
Males	*No evidence of carcinogenic octivity*	*Clear evidence of carcinogenic activity*
Basis		Increased incidences of liver neoplasms and renal tubule neoplasms
Females	*No evidence of carcinogenic activity*	*Clear evidence af carcinogenic activity*
Basis		Increased incidence of liver neoplasms
F344/N rats	0, 50, or 100 mg/kg	0, 16, 32, and 64 mg./kg
Males	*No evidence of carcinogenic activity*	*No evidence of carcinogenic activity*
Basis		
Females	*No evidence of carcinogenic octivity*	*Na evidence of carcinogenic activity*
Basis		

Abbreviations: DEA, diethanolamine; NTP, National Toxicology Program.

NTP, using $B6C3F_1$ mice and F344/N rats.[8] Groups of 50 male and 50 female mice were dosed dermally with 0, 100, or 200 mg/kg cocamide DEA in ethanol, 5 days/wk, for 104 to 105 weeks. There were no statistically significant differences in survival between the test animals and the controls. Mean bws of 100 and 200 mg/kg females were less than controls from weeks 93 and 77, respectively. Dermal irritation was observed at the application site of 200 mg/kg males. The incidences of epidermal and sebaceous gland hyperplasia and hyperkeratosis were statistically significantly greater in all dose groups compared to the controls, and in the in 200 mg/kg dose group, the incidences of ulceration in males and inflammation and parakeratosis in females were increased. The incidences of hepatic neoplasms were statistically significantly greater in dosed male and female mice compared to controls. The incidences of eosinophilic foci in dosed groups of males were increased compared to controls, and the incidence of nephropathy was statistically significant. The incidences of renal tubule adenoma and of renal tubule adenoma or carcinoma (combined) in 200 mg/kg males were statistically significantly greater than controls and exceeded the historical control ranges for these neoplasms. In the thyroid gland, the incidences of follicular cell hyperplasia in all dosed groups of males and females were statistically significantly greater than the controls. The researchers concluded that the clear evidence of carcinogenic activity in male and female $B6C3F_1$ mice was associated with the concentration of free DEA present as a contaminant in the DEA test compound.

Groups of 50 males and 50 females rats were dosed dermally with 0, 50, or 100 mg/kg bw cocamide DEA in ethanol (0, 85, or 170 mg/mL, respectively), 5 days/wk for 104 weeks. Survival and mean bws were similar in test and control animals. Dermal irritation was observed at the application site of 100 mg/kg females. The incidences of epidermal and sebaceous gland hyperplasia, parakeratosis, and hyperkeratosis were statistically significantly greater in all dose groups compared to the controls; the severity of the lesions generally increased with increasing dose and ranged from minimal to mild. Incidences of renal tubule hyperplasia in dosed females and of renal tubule adenoma or carcinoma (combined) in females of the 50 mg/kg group were statistically significantly greater than in the controls. Incidences of nephropathy were similar between test and control rats; severity in females increased with increasing dose. In the forestomach, the incidences of chronic, active inflammation, epithelial hyperplasia, and epithelial ulcer were statistically significantly increased in 100 mg/kg females. The incidence of pancreatic acinar atrophy was statistically significantly greater in the 100 mg/kg males than in the controls. The researchers concluded there was no evidence of carcinogenic activity in male F344/N rats dosed dermally with 50 or 100 mg/kg cocamide DEA. There was equivocal evidence of carcinogenic activity in

female F344/N rats, based on a marginal increase in the incidences of renal tubule neoplasms.

Lauramide DEA

The NTP evaluated the carcinogenic potential of lauramide DEA (90% purity; 0.83% free DEA by weight) using $B6C3F_1$ mice and F344/N rats.[7] Groups of 50 male and 50 female mice were dosed dermally with 0, 100, or 200 mg/kg/d lauramide DEA in ethanol (0, 50, or 100 mg/mL, respectively), 5 days/wk, for 105 to 106 weeks. No clinical findings were attributable to lauramide DEA. In female mice, the incidence of hepatocellular adenoma was statistically significantly increased in the 100 mg/kg group, and eosinophilic foci were statistically significantly increased in the 200 mg/kg group. The incidences of these lesions in male mice were not statistically significantly different from controls. Incidences of nonneoplastic lesions of the skin at the site of application were statistically significantly increased in treated males and females; the lesions were mostly epidermal and sebaceous gland hyperplasia. The incidence of focal hyperplasia of thyroid gland follicular cells was statistically significantly greater in males of the 200 mg/kg group compared to controls; there were no corresponding increases in the incidences of follicular cell neoplasms. There was no evidence of carcinogenic activity in male mice. Researchers hypothesized that evidence of carcinogenic activity in female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms was associated with free DEA that was present as a contaminant.

Groups of 50 male and 50 female rats were dosed dermally with 0, 50, or 100 mg/kg bw lauramide DEA in ethanol (0, 85, or 170 mg/mL, respectively), 5 days/wk, for 104 to 105 wks. Findings showed minimal to moderate irritation at the application site; epidermal and sebaceous gland hyperplasia, hyperkeratosis, and chronic inflammation were statistically significantly increased compared to controls. The incidence of neoplasms was similar for treated and control rats. The incidence of forestomach ulcer in the 100 mg/kg group males, inflammation of the nasal mucosa in all test males, and chronic inflammation of the liver in 100 mg/kg females was statistically significantly lower than that in the controls. There was no evidence of carcinogenic activity of lauramide DEA in male or female F344/rats.

Oleamide DEA

The NTP also examined the carcinogenic potential of dermally applied oleamide DEA (47.5% oleic acid DEA test compound content; 0.19% free DEA) using $B6C3F_1$ mice and F344/N rats.[10] Groups of 55 male and 55 female mice were dosed dermally with 0, 15, or 30 mg/kg oleamide DEA in ethanol (0, 7.5, or 15 mg/mL, respectively), 5 days/wk, for 105 weeks; 5 males and 5 females per group were used for a 3-month interim evaluation. Survival was similar for treated and control mice. Mean bws of females of the 30 mg/kg group were less than controls as of week 76 of the study. Increased incidence of dermal irritation was observed at the application site of males of the 30 mg/kg dose group. The incidences of epidermal and sebaceous gland hyperplasia were statistically significantly increased in all male and female dose groups, when compared to controls, at both the 3-mnth and 2-year evaluation. Additional dermal lesions were observed, but a dose-related increase in neoplasms was not observed. The incidence of malignant lymphoma in female mice increased with increasing dose and was statistically significant in the high-dose group. However, the researchers noted that the incidence in the high-dose group was similar to the incidences observed in other studies that used ethanol as the vehicle. No evidence of carcinogenic activity was found in male or female mice dosed dermally with $\leq$30 mg/kg oleamide DEA.

Groups of 50 male and 50 female rats were dosed dermally with 0, 50, or 100 mg/kg oleamide DEA in ethanol (0, 85, or 170 mg/mL, respectively), 5 days/wk, for 104 weeks. Mean bws of males of the 100 mg/kg group were slightly less than the controls throughout the study and in the females (100mg/kg group), a decrease in bws was observed from week 24 onward. Mild to moderate irritation was observed, and skin lesions observed at the application site, including statistically significant increases in epidermal and sebaceous hyperplasia, were considered indicative of local irritation, with no neoplastic or preneoplastic changes. Researchers did not consider increased incidences of lesions in the forestomach, testis, and thyroid gland test article related. No evidence of carcinogenic activity in male or female rats dosed dermally with $\leq$100 mg/kg oleamide DEA was observed.

Irritation and Sensitization

Dermal Irritation

Non-Human

Cocamide DEA. Cocamide DEA, 30% in propylene glycol, was a moderate skin irritant in an irritation study using an occlusive covering.[2]

Lauramide DEA. In immersion tests using guinea pigs, a 0.1%-0.5% aq solutions of lauramide DEA was minimally to mildly irritating, a shampoo formulation containing 8% lauramide DEA, tested as a 0.5% solution, was a slight irritant, and a bubble bath containing 6% lauramide DEA, tested as a 0.5% aq solution, was practically nonirritating. In rabbits, a 1.25% to 10% aq solution was practically nonirritaing to slightly irritating, while a 20% aq solution was a severe irritant. In a 14-day cumulative irritation test using rabbits, a 1% aq solution was not an irritant, a 5% solution was a moderate irritant, and a 25% solution was a severe irritant. Liquid soap formulations containing 10% lauramide DEA ranged from mildly to severely irritating in rabbit skin.[2]

Stearamide DEA. A mixture containing 35% to 40% stearamide DEA had a primary irritation score of 0 in a dermal study using rabbits.[3]

Oleamide DEA. Oleamide DEA in propylene glycol was mildly irritating to rabbit skin when tested at 5% and moderately irritating when tested at 70%.[2]

Linoleamide DEA. A 0.1% to 0.5% aq solution of linoleamide DEA was nonirritating to slightly irritating in immersion tests with guinea pigs, and a formulation containing 1.5% linoleamide DEA, tested as a 0.5% aq. solution, was a slight irritant in an immersion test. In primary irritation tests using rabbits, 5% to 10% aq linoleamide DEA was nonirritating to mildly irritating, while an aq solution of 20% linoleamide DEA was a severe dermal irritant in rabbits. A formulation containing 1.5% linoleamide DEA, tested as a 2.5% aq solution, was a minimal dermal irritant in rabbits.[2]

Ricinoleamide DEA. Undiluted polyethylene glycol (PEG)-20 glyceryl ricinoleate + ricinoleamide DEA was evaluated for dermal irritation in a Draize test using NZW rabbits.[34] A semi-occlusive patch with 0.5 g of the test material was applied to a 6 cm^2 shaved site on the dorsal area of the trunk for 4 hours. No signs of irritation were observed, and the surfactant was nonirritating.

Human

Cocamide DEA. The irritation potential of 10% cocamide DEA, 20% sodium lauryl sulfate, and 5 other cosmetic-grade surfactant solutions was evaluated in 15 patients. Adverse reactions were not observed. Researchers concluded that skin irritation was not related to the total concentration of the surfactants in contact with the skin but rather the combination of surfactants present.[1]

An aq solution of 12.5 mmol/L cocamide DEA was applied to the forearm of 15 volunteers.[35] Using a plastic chamber, a 0.3 mL solution was applied for 45 min/exposure twice a day, 5 days/wk, for a total of 28 applications. The mean transepidermal water loss (TEWL) with cocamide DEA was 7.0 g/m^2 l; the TEWL with 12.5 mmol/L sodium lauryl sulfate was 15.2 g/m^2 l.

The irritation potential of 0.5% aq cocamide DEA was evaluated in a single insult occlusive patch test using 105 patients, 14.3% of which were atopic patients.[36] Application of 40 μL was using Haye test chambers for 48 hours; the test site was evaluated by erythema and edema. An untreated occlusive patch was used as a negative control. Cocamide DEA had a total average index of skin irritation (AII) of 0.065 and was nonirritating (AII < 0.5) based on an amended Draize scale.

Lauramide DEA. In primary irritation tests (single patch) using 17 to 19 patients, a 1.25% aq solution of a shampoo containing 8%, and a bubble bath containing 6% lauramide DEA, and an unspecified product containing 5% lauramide DEA, tested as a 1% aq solution, minimal to mild irritation was observed. In 3 cumulative irritation soap chamber tests using 12 to 15 patients, liquid soap formulations containing 10% lauramide DEA, tested as 8% aq solutions, were essentially nonirritating to mildly irritating. In a 21-day cumulative irritation study, a medicated liquid soap containing 5% lauramide DEA, tested as a 25% solution, was a moderate skin irritant. A liquid soap containing 10% lauramide DEA, evaluated in 114 patients for 4 weeks, was minimally irritating under normal use and an acne liquid cleanser containing 5% lauramide DEA, evaluated in 50 patients with twice daily use for 6 weeks, was a mild irritant.[2]

Linoleomide DEA. In a primary irritation (single patch) study, a product containing 1.5% linoleamide DEA, tested as a 1.25% aq solution in 20 patients, was a mild skin irritant.[2]

Sensitization

Human

Cocamide DEA. In 8 occupational exposure studies to evaluate the sensitization potential of cocamide DEA at 0.01% to 10%, positive results were seen; however, it is recognized that while occupational exposure to cocamide DEA can result in sensitization, cosmetic use does not present the same concerns.[1] An in-use study using shampoo containing 2% cocamide DEA on104 female patients patch tested with 2% aq shampoo before and 10 days after 87 days of using the shampoo showed that cocamide DEA was an irritant but not a sensitizer.[2]

Lauramide DEA. Six repeat insult patch tests (RIPTs) using 41 to 159 patients were performed on formulations containing 4% to 10% lauramide DEA, as 0.25% to 1.25% solutions. Lauramide DEA was not a sensitizer in any of the studies.[2]

Linoleamide DEA. In an RIPT conducted with 100% linoleamide DEA on 100 patients, no irritation or sensitization reactions were observed. A dandruff shampoo containing 1.5% linoleamide DEA, tested as a 1% aq solution in a RIPT using 101 patients, was an irritant but not a sensitizer.[2]

Provocative Testing

Cocamide DEA. Metalworkers with dermatitis were patch tested with 0.5% cocamide DEA in pet.[37] The patches were applied for 1 to 2 days. Of the 215 patients, 1 (0.5%) had a positive reaction on day 3.

Coreactivity

Cocamide DEA. Thirty-five patients that had positive patch tests to cocamidopropyl betaine, amidoamine, or both, were tested for coreactivity with cocamide DEA.[38] Two (5.7%) of the patients had positive reactions to cocamide DEA.

Case Studies

Cocamide DEA. In all, 1 patient with dermatitis on the hands and face, and 2 with dermatitis on the hands and forearms, were patch tested using the North American Contact Dermatitis Group standard tray and supplemented with additional chemicals.[39] All the 3 patients had either personal or industrial exposure to cocamide DEA-containing products. All 3 had positive patch test results (2+) to cocamide DEA, and 2 had reactions to several other chemicals. In all patients, the dermatitis cleared with avoidance of cocamide DEA-containing products.

Undecylenamide DEA. One patient with dermatitis of the hands and axillae had positive test reaction to a liquid soap.[40] Subsequent testing with 0.1% and 1% aq undecylenamide

DEA, an ingredient in the soap, gave positive reactions. In 10 control patients, testing with 0.1% undecylenamide DEA was negative.

Phototoxicity/Photosensitization

Human

Lauramide DEA. A 10% solution of lauramide DEA, tested in 25 patients, was not phototoxic. In a photosensitivity study of 10% lauramide DEA, tested as a 1% aq solution in 25 patients, slight irritation was seen in 9 patients at induction and 4 at challenge. The test substance was not a photosensitizer.[2]

Ocular Irritation

In Vitro

Cocamide DEA. A 10% solution of Cocamide DEA, classified as a nonirritant to minimal ocular irritant, was evaluated in the EpiOcular tissue model. The irritation classification, compared to the results of a Draize test, was similar to a nonirritant score obtained in the Draize test.[41]

Myristamide DEA. When Myristamide DEA was evaluated in a neutral red assay, the IC_{50} values in Chinese hamster fibroblast V79 cells, rabbit corneal cells, and human epidermal keratinocytes were 15.2, 23.9, and 6.2 μg/mL, respectively. The DS_{20} (concentration predicted to produce a Draize score of 20/110) was 14.4% w/w myristamide DEA.[3]

Non-Human

Cocamide DEA. A solution of >64% cocamide DEA and <29% DEA was a severe irritant in rabbit eyes.[1] In another study, a solution of Cocamide DEA, 30% in propylene glycol, was a mild eye irritant in rabbits. [2]

Lauramide DEA. Five ocular irritation studies were performed in rabbits with lauramide DEA at concentrations of 1% to 25%. Lauramide DEA 1 % aq was mildly irritating, 5% was slightly to moderately irritating, 10% to 20% was moderately irritating, and 25% was moderately to severely irritating. One bubble bath formulation containing 6% lauramide DEA was practically nonirritating, while another was moderately irritating, and 3 shampoo formulations containing 8% lauramide DEA were nonirritating to moderately irritating. In a mucous membrane irritation test, a soap containing 10% lauramide DEA was significantly more irritating than water to vaginal mucosa of rabbits.[2]

Stearamide DEA. A mixture containing 35% to 40% stearamide DEA was not irritating to rabbit eyes.[3]

Isostearamide DEA. A formulation containing 8.0% isostearamide DEA was a moderate irritant in rabbit eyes.[3]

Oleamide DEA. Undiluted oleamide DEA was practically nonirritating to rabbit eyes.[2]

Linoleamide DEA. An aq solution (10 %) administered to rabbit eyes was practically nonirritating, and an undiluted solution was minimally to moderately irritating. A product containing 1.5% linoleamide DEA, applied as a 25% aq solution, and a formulation containing 15% linoleamide DEA were moderate eye irritants in rabbits, while a formulation containing 15% linoleamide DEA, applied as a 25% aq solution, was mildly irritating.[2]

Ricinoleamide DEA. Undiluted PEG-20 glyceryl ricinoleate + ricinoleamide DEA (amount present was not stated) was evaluated for ocular irritation using NZW rabbits.[34] No signs of irritation were observed, and the surfactant was a nonirritant.

Summary

This safety assessment includes 33 DEAs as used in cosmetics. Information on some of these ingredients reviewed previously by CIR is included here to fill noted gaps in the available safety data and to create a report on the complete family of ingredients. Cocamide DEA and most of the other diethanolamides are reported to function in cosmetic formulations as a surfactant foam booster or a viscosity increasing agent, although a few are reported to function as a hair and skin conditioning agent, surfactant-cleansing or emulsifying agent, or an opacifying agent.

The DEAs consist of covalent, tertiary amides where 2 of the nitrogen substituents are ethanol (or at least an ethanol residue) and the third is a carbonyl-attached substituent. These ingredients are not salts and do not readily dissociate in water. Amidases, such as fatty acid amide hydrolase which is known to be present in human skin, could potentially convert the diethanolamides to DEA and the corresponding fatty acids. The yield of DEA from metabolism of diethanolamides in human skin is unknown.

The diethanolamides generally have some amount of free DEA, and that amount can vary greatly by ingredient. For example, in the NTP studies, it was estimated that oleamide DEA contained 0.19% free DEA, while cocamide DEA contained 18.2% free DEA by weight.

The VCRP data obtained in 2011 indicate that cocamide DEA is used in 710 cosmetic formulations, the majority of which are rinse-off formulations. With the exception of lauramide DEA, which is reported to be used in 281 cosmetic formulations, the remaining diethanolamides have less than 35 uses, and most are not reported to be used. The reported concentration of use of the diethanolamides ranges from 0.2% to 12%; the greatest leave-on concentration reported was 9%. Fatty acid dialkanolamides are allowed for use in products in Europe with restrictions; the restrictions address secondary amine content.

[^{14}C]Lauramide DEA partitioned well into rat and human liver slices, and the absorbed radioactivity was mostly unchanged lauramide DEA. In the media, 18% to 42% of the radioactivity was present in the form of metabolites. Using microsomes to compare hydroxylation, lauramide DEA 12-hydroxylase activity in human liver microsomes was similar to that in rat liver microsomes, but 3 times the rate observed in rat kidney microsomes.

Mice and rats were exposed dermally to 5 to 800 mg/kg and 25 or 400 mg/kg [^{14}C]lauramide DEA, respectively. Absorption in rats was similar for each dose when calculated as a percentage of dose, and absorption was greater in mice (50%-70% of the applied dose) than in rats (20%-24%). The parent compound and the half-acid amide metabolites were detected in the plasma of rats. Repeated application of 25 mg/kg/d lauramide DEA did not appear to affect absorption or excretion. In rats dosed orally with 1000 mg/kg [^{14}C]lauramide DEA, 4% of the dose was recovered in the tissues and 79% in the urine after 72 hours; at 6 h, no DEA, DEA metabolites, or unchanged lauramide DEA were found in the urine; only very polar metabolites were found. With iv dosing, a 50 mg/kg dose of lauramide DEA was quickly metabolized and eliminated by mice; approximately 95% of the dose was excreted in the urine in 24 hours. More than 80% of a 25 mg/kg dose was excreted in the urine by rats in 24 hours.

Acute dermal testing with undiluted cocamide and lauramide DEA, 50% lauramide DEA, and undiluted and 10% aq linoleamide DEA and acute oral testing with several fatty acid diethanolamides did not result in notable toxicity. In an acute inhalation toxicity study with 86 to 219 mg/m^3 tallamide DEA in rats, low concentration produced sensory and pulmonary irritation. The LC_{50} value was >219 mg/m^3.

In repeated dose dermal studies with cocamide, lauramide, and oleamide DEA in mice and/or rats, irritation was observed at the site of application. Increases in liver and kidney weights were observed in most studies, while decreases in bw were observed sporadically. The incidence of renal tubule regeneration was greater in female rats dosed with 100 to 400 mg/kg cocamide DEA when compared to controls. A formulation containing 3% linoleamide DEA was not a cumulative systemic toxicant in a 13-week dermal study; dermal irritation was observed.

With repeat oral dosing of lauramide DEA, the NOEL was 0.1% in feed in a study with SPF rats and 250 mg/kg/d in a feeding study using Wistar rats. The NOEL for Beagle dogs fed lauramide DEA for 12 weeks was 5000 ppm.

In a developmental toxicity study in Sprague-Dawley rats, the NOAEL for maternal toxicity and developmental toxicity was 1000 mg/kg/d that was the highest dose tested. No other data on the reproductive and developmental toxicity of the diethanolamides were found. Available reproductive and developmental toxicity data on DEA and some of the fatty acids from previous CIR reports show no significant toxic effects noted. For DEA, the NOEL for embryonal/fetal toxicity with dermal application was 380 mg/kg/d for rats and 350 mg/kg/d for rabbits. In one oral study, the NOEL for embryonal/fetal toxicity was 200 mg/kg/d in rats, and in another, the LOAEL for both maternal toxicity and teratogenicity was 125 mg/kg/d in rats. In an inhalation study, in rats, the NOAEC for both maternal and developmental toxicity was 0.05 mg/L, and the NOAEC for teratogenicity was >0.2 mg/L.

Cocamide DEA, lauramide DEA, and oleamide DEA were, generally, nongenotoxic in a number of assays. There was an increase in the frequency of micronucleated erythrocytes in mice by cocamide DEA and the induction of SCEs in CHO cells by lauramide DEA.

The carcinogenic potential of dermally applied cocamide, lauramide, and oleamide DEA was evaluated in B6C3F$_1$ mice and F344/N rats in an NTP study. Cocamide DEA produced carcinogenic activity (hepatic and renal tubule neoplasms) in male and female mice (100-200 mg/kg), equivocal evidence (renal tubule neoplasms) in female rats (50-100 mg/kg), and no evidence in male rats (50-100 mg/kg). Lauramide DEA produced evidence of carcinogenic activity (hepatocellular neoplasms) in female mice (100-200 mg/kg), and no evidence in male mice (100-200 mg/kg) or male and female rats (50-100 mg/kg). Oleamide DEA produced no evidence of carcinogenic activity in male or female mice (15-30 mg/kg) or male or female rats (50-100 mg/kg).

The dermal irritation of fatty acid diethanolamides, in nonhuman and human testing, varied greatly with formulation and test conditions. Lauramide DEA and linoleamide DEA were not sensitizers in humans. Cocamide DEA, 0.01% to 10%, produced positive results in provocative sensitization studies. Lauramide DEA was not phototoxic in humans. The ocular irritation of fatty acid also varied greatly with formulation and test conditions.

Discussion

The CIR Expert Panel agreed to reopen the review of cocamide DEA, and add 32 similar diethanolamides. Some of the ingredients included in this rereview, specifically isostearamide DEA, lauramide DEA, linoleamide DEA, myristamide DEA, oleamide DEA, and stearamide DEA, have been reviewed by the CIR in the past. Although the Panel noted gaps in the available safety data for many of the diethanolamides included in this group, the Panel was able to extrapolate the existing data, including the data from previous CIR assessments as well as recently published data, to support the safety of all the diethanolamides included in this safety assessment. Similar structure–activity relationships and functions made that extrapolation feasible.

The Panel expressed concern about the lack of reproductive and developmental toxicity data for most of the diethanolamides. Since DEA may be present as an impurity in the diethanolamides, and because amidases in the skin might convert some of the diethanolamides to DEA and the corresponding fatty acid, the Panel determined that data from the CIR safety assessment on DEA as well as from assessments on the other "components" was applicable. The lack of reproductive toxicity for DEA or any of the components alleviated this concern.

The Panel was also concerned with levels of free DEA that could be present as an impurity in diethanolamides. The Panel reasoned that the "clear evidence of carcinogenic activity" of cocamide DEA reported for male and female mice and the "equivocal evidence of carcinogenic activity" of cocamide DEA reported in female rats, as well as "some evidence of carcinogenic activity" of lauramide DEA in female mice, was due to the presence of free DEA. This opinion was supported

by carcinogenicity studies showing that the level of carcinogenic activity in cocamide DEA, lauramide DEA, and oleamide DEA corresponded to the amount of free DEA found in the test substance. The Panel stated that the amount of free DEA available in diethanolamides must be limited to the present practices of use and concentration of DEA itself. The Panel was also concerned that free DEA present as an impurity in the diethanolamides could be converted (nitrosated) into N-nitrosamines that may be carcinogenic. Consequently, they recommended that diethanolamides should not be used in cosmetic products in which N-nitroso compounds can be formed.

Studies showed that products formulated using diethanolamides are potential dermal irritants. The Expert Panel specified that products must be formulated to be nonirritating.

Because some of the ingredients named in the assessment can be used in products that may be sprayed, the Panel discussed the issue of potential inhalation toxicity. In the absence of sufficient safety test data to evaluate this end point directly, the Panel considered other data that were available to characterize the potential for the diethanolamides to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects. The Panel noted that 95% to 99% of particles produced in cosmetic aerosols are not respirable. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

Conclusion

The CIR Expert Panel concluded that the following 33 diethanolamides are safe in the present practices of use and concentration described in this safety assessment (ingredients not in current use are identified with *), when formulated to be nonirritating, and when the levels of free DEA in the diethanolamides do not exceed the present practices of use and concentration of DEA itself. The Expert Panel cautions that ingredients should not be used in cosmetic products in which N-nitroso compounds can be formed.

Almondamide DEA*
Apricotamide DEA*
Avocadamide DEA*
Babassuamide DEA*
Behenamide DEA*
Capramide DEA
Cocamide DEA
Cornamide DEA*
Cornamide/Cocamide DEA*
Hydrogenated Tallowamide DEA*
Isostearamide DEA
Lanolinamide DEA*
Lauramide DEA
Lauramide/Myristamide DEA
Lecithinamide DEA*
Linoleamide DEA
Minkamide DEA*
Myristamide DEA
Oleamide DEA
Olivamide DEA*
Palm Kernelamide DEA
Palmamide DEA*
Palmitamide DEA*
Ricebranamide DEA*
Ricinoleamide DEA*
Sesamide DEA*
Shea Butteramide/Castoramide DEA*
Soyamide DEA
Stearamide DEA
Tallamide DEA*
Tallowamide DEA*
Undecylenamide DEA*
Wheat Germamide DEA

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th St, Suite 412, Washington, DC 20036, USA.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The articles in this supplement were sponsored by the Cosmetic Ingredient Review. The Cosmetic Ingredient Review is financially supported by the Personal Care Products Council.

References

1. Andersen FA (ed). Amended final report on the safety assessment of cocamide DEA. *J Am Coll Toxicol.* 1996;15(6):527-542.
2. Elder RL (ed). Final report on the safety assessment of cocamide DEA, lauramide DEA, linoleamide DEA, and oleamide DEA. *J Am Coll Toxicol.* 1986;5(5):415-454.
3. Pang S. Isostearamide DEA & MEA, Myristamide DEA & MEA, Stearmide DEA & MEA. 1995. Available from the CIR, 1101 17th Street, NW, Ste 412, Washington DC 20036. http://cir-safety.org.
4. Bíró T, Tóth BI, Haskó G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. *Trends Pharmacol Sci.* 2009;30(8):411-420.
5. Bisogno T, De Petrocellis L, Di Marzo V. Fatty acid hydrolase, an enzyme with many bioactive substrates. Possible therapeutic implications. *Current Pharm Des.* 2002;8(7):125-133.
6. Gray GM, Tabiowo A, Trotter MD. Studies on the soluble membrane-bound amino acid 2-naphthylamidases in pig and human epidermis. *Biochem J.* 1977;161(3):667-675.
7. National Toxicology Program. NTP Technical report on the toxicology and carcinogenesis studies of lauric acid diethanolamine

condensate (CAS No. 120-40-1) in F344/N rats and B6C3F$_1$ mice. (Dermal studies.) NTP TR 480. 1999.
8. National Toxicology Program. NTP Technical report on the toxoicology and carcinogenesis studies of coconut oil acid diethanolamine condensate (CAS No. 68603-42-9) in F344/N rats and B6C3F$_1$ mice. (Dermal studies.) NTP TR 479. 2001.
9. Chou HJ. Determination of diethanolamine and N-nitrosodiethanolamine in fatty acid diethanolamides. *J Assoc Off Anal Chem Intl.* 1998;81(5):943-947.
10. National Toxicology Program. NTP Technical report on the toxicology and carcinogenesis studies of oleic acid diethanolamine condensate (CAS No. 93-83-4) in F344/N rats and B6C3F$_1$ mice. (Dermal studies.) NTP TR 481. 1999.
11. Gottschalck TE, Bailey JE. eds. *International Cosmetic Ingredient Dictionary and Handbook.* Washington, DC: Personal Care Products Council; 2010.
12. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* Washington, DC: FDA; 2011.
13. Personal Care Products Council. Updated concentrationi of use by FDA product category: Dialkanolamides. 2011. Unpublished data submitted by the Council on May 17, 2011. (2 pp).
14. Personal Care Products Council. Concentration of use: oliveamide DEA. 2011. Unpublished data submitted by the Council on May 31, 2011. (1 p).
15. Johnsen MA. The influence of particle size. *Spray Technol Marketing.* 2004;November:24-27.
16. Rothe H. Special aspects of cosmetic spray evalulation. 2011. Unpublished data presented at the CIR Expert Panel meeting on September 26, 2011. Washington, DC.
17. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: principles on inhalation risk assessment. *Toxicol Lett.* 2011;205(2):97-104.
18. Bremmer HJ, Prud'homme de Lodder LCH, Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. Report No. RIVM 320104001/2006. 1-77.
19. European Commission. Cosing Database. [EC Regulation (v.2)] Annex III/1, 60; fatty acid dialkylamides and dialkanolamides. http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=28311&back=1. Accessed April 29, 2011.
20. European Commission. CosIng Database (Cosmetics Directive v. 1). http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.simple. Accessed April 29, 2011.
21. Food and Drug Administration. Everything Added to Food in the United States (EAFUS). http://www.fda.gov/Food/FoodIngredientsPackaging/ucm115326.htm. Accessed January 30, 2011.
22. Environmental Protection Agency. Screening-level hazard characterization, Fatty nitrogen derived (FND) amides category. 2010. http://www.epa.gov/chemrtk/hpvis/hazchar/Category_FND%20Amides_September_2010.pdf. Accessed January 29, 2011. Summaries of unpublished data.
23. Mathews JM, DeCosta K, Thomas BF. Lauramide diethanolamine absorption, metabolism, and disposition in rats and mice after oral, intravenous, and dermal administration. *Drug Metab Dispos.* 1996;24(7):702-710.
24. Merdink J, Decosta K, Mathews JM, Jones CB, Okita JR, Okita RT. Hydroxylation of lauramide diethanolamine by liver microsomes. *Drug Metab Dispos.* 1996;24(2):180-186.
25. Environmental Protection Agency. Appendix 1. Robust summaries. ACC FND Amides Category 1 - FND Amides. 9-16-2004. http://www.epa.gov/hpv/pubs/summaries/fantdrad/c13319rr.pdf. Accessed January 29, 2011. Summaries of unpublished data.
26. Consumer Product Testing. Acute oral toxicity study on cocamide DEA in rats. http://iaspub.epa.gov/oppthpv/document_api.download?FILE=Robust Summary 1.pdf. Accessed January 25, 2011.
27. Elder RL (ed). Final report on the safety assessment of triethanolamine, diethanolamine, and monoethanolamine. *J Am Coll Toxicol.* 1983;2(7):183-235
28. Fiume MM. Final amended report on the safety assessment of diethanolamine and its salts as used in cosmetics. Available from the Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036. www.cir-safety.org.
29. Andersen FA (ed). Final report on the safety assessment of lecithin and hydrogenated lecithin. *Int J Toxicol.* 2001;20(suppl 1):21-45.
30. Andersen FA (ed). Final report on the safety assessment of elaeis guineensis (palm) oil, elaeis guineensis (palm) kernel oil, hydrogenated palm oil and hydrogenated palm kemel oil. *Int J Toxicol.* 2011;19(suppl 2):7-28.
31. Andersen FA (ed). Final report on the safety assessment of ricinus communis (castor) seed oil, hydrogenated castor oil, glyceryl ricinoleate, glyceryl ricinoleate se, ricinoleic acid, potassium ricinoleate, sodium ricinoleate, zinc ricinoleate, cetyl ricinoleate, ethyl ricinoleate, glycol ricinoleate, isopropyl ricinoleate, methyl ricinoleate, and octyldodecyl ricinoleate. *Int J Toxicol.* 2011;26(suppl 3):31-77.
32. Johnson W, Jr, Bergfeld WF, Belsito DV, et al. Amended safety assessment of sesamum indicum (sesame) seed oil, hydrogeanted sesame seed oil, sesamum indicum (sesame) oil unsaponifiables, and sodium sesameseedate. *Int J Toxicol.* 2011;30(suppl 3):40S-53S.
33. Robinson V, Bergfeld WF, Belsito DV, et al. Amended safety assessment of tall oil acid, sodium tallate, potasstium tallate, and ammonium tallate. *Int J Toxicol.* 2009;28(suppl 3):252S-258S.
34. Corsini E, Marinovich M, Marabini L, Chiesara E, Galli CL. Interleukin-1 production after treatment with non-ionic surfactants in a murine keratinocytes cell line. *Toxicol In Vitro.* 1994;8(3):361-369.
35. Tupker RA, Pinnagoda J, Coenraads PJ, Nater JP. The influence of repeated exposure to surfactants on the human skin as determined by transepidermal water loss and visual scoring. *Contact Dermatitis.* 1989;20(2):108-114.
36. Corazza M, Lauriola MM, Bianchi A, Zappaterra M, Virgili A. Irritant and sensitizing potential of eight surfactants commonly used in skin cleansers: an evaluation of 105 patients. *Dermatitis.* 2010;21(5):262-268.
37. Geier J, Lessmann H, Frosch PJ, et al. Patch testing with components of water-based metalworking fluids. *Contact Dermatitis.* 2003;49(2):85-90.

38. Brey NL, Fowler JF. Relevance of positive patch-test reactions tp cocamidopropyl betaine and amidoamine. *Dermatitis*. 2004; 15(1):7-9.
39. Fowler JF. Allergy to cocamide DEA. *Am J Contact Dermat*. 1998;9(1):40-41.
40. Christersson S, Wrangsjo K. Contact allergy to undecylenamide diethanolamide in a liquid soap. *Contact Dermatitis*. 1992;27(3): 191-192.
41. Stern M, Klausner M, Alvarado R, Renskers K, Dickens M. Evaluation of the EpiOcular tissue model as an alternative to the Draize eye irritation test. *Toxicol In Vitro*. 1998;12(4):455-461.
42. Burnett CL, Fiume MM. Final report of the CIR Expert Panel on the safety of plant-derived fatty acid oils and used in cosmetics. 2011. Available from the CIR, 1101 17th Street, NW, Ste 412, Washington DC 20036. http://cir-safety.org.
43. Elder RL (ed). Final report on the safety assessment of isostearic acid. *J Am Coll Toxicol*. 1986;2(7):61-74.
44. Elder RL (ed). Final report on the safety assessment for acetylated lanolin alcohol and related compounds. *JEPT*. 1980;4(4):63-92.
45. Elder RL (ed). Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. *J Am Coll Toxicol*. 1987;6(3):321-401.
46. Andersen FA (ed). Final amended report on the safety of mink oil. *Int J Toxicol*. 2005;24(suppl 3):57-64.
47. Becker LC, Bergfeld WF, Belsito DV, et al. Final report on the amended safety assessment of myristic acid and its salts and esters as used in cosmetics. *Int J Toxicol*. 2010;29(suppl 3):162S-186S.
48. Elder RL (ed). Final report on the safety assessment of tallow, tallow glyceride, tallow glycerides, hydrogenated tallow glyceride, and hydrogenated tallow glycerides. *J Am Coll Toxicol*. 1990; 9(2):153-164.
49. Advanced Chemistry Development (ACD/Labs). Advanced Chemistry Development software v11.02. 2011. ((C) 1994-2011 ACD/Labs).
50. National Toxicology Program. Toxicology and carcinogenesis studies of diethanolamine (CAS No. 111-42-2) in F344/N rats and B6C3F$_1$ mice. (Dermal studies.) NTP TR 478. 1999. Report No. NTIS PB99-167553.

2019 VCRP DATA – ALKYL AMIDE MIPA

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

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: September 11, 2019

SUBJECT: Draft Tentative Report: Safety Assessment of Alkyl Amide MIPA Ingredients as Used in Cosmetics (draft prepared for the September 16-17, 2019 CIR Expert Panel meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Alkyl Amide MIPA Ingredients as Used in Cosmetics.

Cosmetic Use; Summary - The Cosmetic Use section and the Summary need to make it clear that the EU inventory of cosmetic ingredients does not list restrictions. The restrictions are listed in the EU cosmetic regulations.

Cosmetic Use - It is not correct to state that "Peanutamide MIPA is also included in Annex III (reference #306)". Reference #306 is actually "Peanut oil, extracts and derivatives". The INCI name Peanutamide MIPA has been associated with reference #306.

Summary - Please correct LD_{40}

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

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: October 24, 2019

SUBJECT: Tentative Report: Safety Assessment of Alkyl Amide MIPA Ingredients as Used in Cosmetics (release date: September 30, 2019)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Alkyl Amide MIPA Ingredients as Used in Cosmetics.

Key Issue

Although the ECHA dossier does not specifically state that the 14-week and the 104-week dermal studies on "amides, C12-18 and C18-unsatd., –(hydroxyethyl)" are the NTP studies on Cocamide DEA, a comparison between the NTP bioassay (at: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr479.pdf) and the studies in the ECHA dossier indicates that they are the same. Both report using the same lot of test material, the source of the animals was the same and the dates the studies were completed were the same. Please cite these studies to the primary reference, the NTP bioassay.

Additional Considerations

Cosmetic Use - It should be made clear that the 0.5 ppm limit for peanut protein is for the raw material. The adaptation that added this entry is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R2228&from=EN.

Acute, Dermal, Isostearamide MIPA - OECD TG 402 is titled "Acute Dermal Toxicity". The objective is to look at acute dermal toxicity, rather than to determine an LD_{50} value as suggested by the CIR report.

Subchronic, Oral, Oleamide MIPA - In several places in the description of the 13-week study of Oleamide MIPA in rats, either an "s" needs to be added to the gender, e.g., "locomotor activity in male[s], or the word rats needs to be added to the gender, e.g., "ptyalism in female [rats]."

Genotoxicity; Summary - Please state the species used in the *in vivo* tests.

Carcinogenicity - The "Please note:..." at the end of the first paragraph should be deleted as the

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

information is now in the subtitle.

Summary - In the Summary, please state the species and duration of the study in which the NOAEL was >750 mg/kg (animals dosed by gavage up to 1500 mg/kg, 5 days/week).

Reference 18 - Please delete the Note associated with reference 18 as the material tested was not always Isostearamide MIPA.