Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 10, 2019
Panel Meeting Date:	June 6-7, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Director
Date: May 10, 2019
Subject: Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics

Enclosed is the draft Final Report on the Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics. (It is identified in the pdf document as *alkfat062019rep*.) At the December meeting, the Panel issued a tentative report with a conclusion that the 40 alkoxylated fatty amides named in the document are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

Concentration of use data were received for PEG-3 Lauramide and PEG-20 Cocamide MEA (*alkfat062019data_1a*; *data_1b*). The data have been included, and the use tables and conclusion have been adjusted accordingly. An exposure assessment submitted by the CIR Science and Support Committee was reviewed at the December meeting; this document was distributed to the Panel the morning of that meeting, but is also included with this submission in case you want to review it again (*alkfat062019data_2*). Comments received from the Council that were received prior to the December 2018 meeting on the draft Tentative Report (*alkfat062019PCPC_1*), and on the Tentative Report that was issued following that meeting (*alkfat062019PCPC_2*), have been addressed.

The following are also included as a part of this report package:

alkfat062019flow: report flowchart
alkfat062019hist: report history
alkfat062019prof: data profile
alkfat062019strat: search strategy
alkfat062019min: transcripts from previous meetings
alkfat062019FDA: 2019 VCRP data

The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, a Final Report should be issued.

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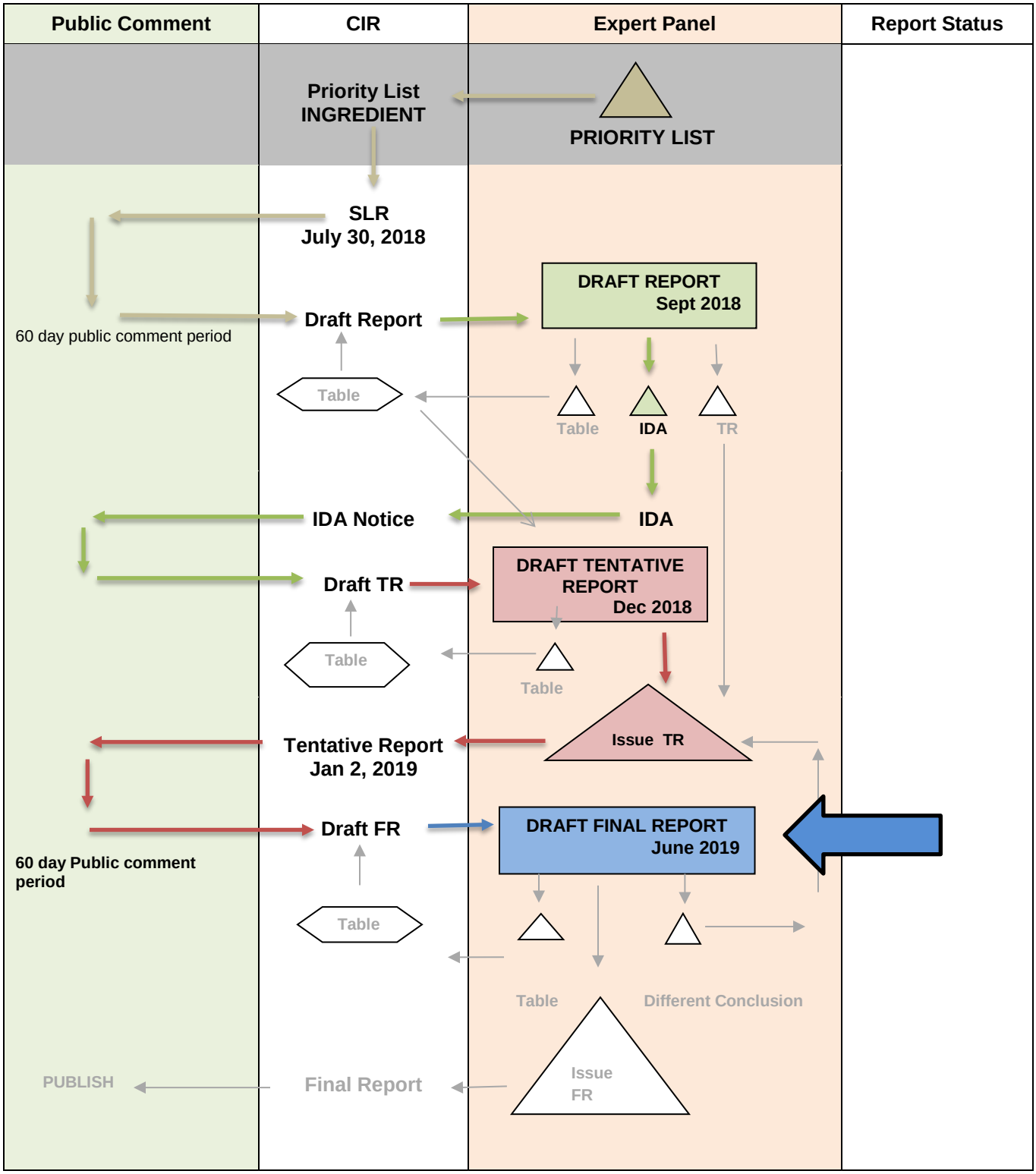
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Alkoxylated Fatty Amides

MEETING June 2019



Report History – Alkoxylated Fatty Amides

July 30, 2018: Scientific Literature Review announced

- Concentration of use data were incorporated into the SLR

September 24-25, 2018: Draft Report

- No additional unpublished data received in response to the SLR
    - The Panel issued an IDA, requesting the following information:
    - Method of manufacture
    - Impurities data
    - Dermal absorption data on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide
        - If absorbed, then 28-day dermal toxicity data, as well as data on other toxicity endpoints, may be needed

December 3-4, 2018: draft Tentative Report

- The ingredient, PEG-5 Oleamide Dioleate, was inadvertently retained in this grouping of ingredients (this grouping comprises secondary amides exclusively, whereas this ingredient is a tertiary amide). Noting our error, we have deleted this ingredient from the report.
- Method of manufacture and impurities data for PEG-50 Hydrogenated Palmamide were received and added to the report
- Updated concentration of use data, and studies of acute dermal toxicity in the rat, skin irritation in rabbits, and skin sensitization in guinea pigs, for PPG-2 Hydroxyethyl Cocamide were also received. However, this information did not change what the Panel already reviewed at the September meeting
- Process description PPG-2 Hydroxyethyl Coco/Isostearamide; PPG-2 Hydroxyethyl Cocamide purity and impurities; and method of manufacture PPG-2 Cocamide were received just prior to the meeting, and were distributed to the Panel
- Exposure assessment data on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide (found in the NICNAS report) were discussed at the meeting, and added to the report
- ***The Panel concluded that the following 40 alkoxylated fatty amides are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating***

June 6-7, 2019: draft Final Report

- Concentration of use data were received for PEG-3 Lauramide and PEG-20 Cocamide MEA, and added to the report

Alkoxylated Fatty Amides* – June 6-7, 2019 Panel Meeting – Writer, 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/log K_{ow}	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
PEG-2 Cocamide	X																												
PEG-3 Cocamide	X																												
PEG-4 Cocamide																													
PEG-5 Cocamide	X																												
PEG-6 Cocamide	X																												
PEG-7 Cocamide																													
PEG-11 Cocamide																													
PEG-20 Cocamide																													
PEG-3 Cocamide DEA																													
PEG-20 Cocamide MEA																													
PEG-6 Hydrogenated Palmamide																													
PEG-50 Hydrogenated Palmamide	X	X	X																										
PEG-13 Hydrogenated Tallow Amide																													
PEG-5 Lanolinamide																													
PEG-2 Lauramide																													
PEG-3 Lauramide	X																												
PEG-5 Lauramide																													
PEG-6 Lauramide	X																												
PEG-11 Lauramide																													
PEG-3 Oleamide																													
PEG-4 Oleamide																													
PEG-5 Oleamide																													
PEG-6 Oleamide																													
PEG-7 Oleamide																													
PEG-9 Oleamide																													
PEG-4 Rapeseedamide	X		X	X			X	X	X		X			X	X	X				X	X		X	X			X		X
PEG-4 Stearamide																													
PEG-10 Stearamide																													
PEG-15 Stearamide																													
PEG-50 Stearamide																													
PEG-5 Tallow Amide																													
PEG-8 Tallow Amide																													
PEG-50 Tallow Amide	X																												
PEG-2 Tallowamide DEA																													

Alkoxylated Fatty Amides* – June 6-7, 2019 Panel Meeting – Writer, 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/log K_{ow}	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
Polyglyceryl-4-PEG-2 Cocamide																												
PPG-2 Cocamide	**X**	X																										
PPG-1 Hydroxyethyl Caprylamide																												
PPG-2 Hydroxyethyl Cocamide	**X**						X	X			X				X	X				X	X		X				X		
PPG-2 Hydroxyethyl Coco/Isostearamide	**X**	X	X																										
PPG-3 Hydroxyethyl Soyamide																													
PPG-2 hydroxyethyl isostearamide (component of Hydroxyethyl Coco/Isostearamide)				X				X							X													

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

Alkoxylated Fatty Amides

Ingredient	CAS #	InfoB	SciFin	FDA	EU	ECHA	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH
Alkoxylated Amides															
PEG-2 Cocamide	----	---	0			0									
PEG-3 Cocamide	61791-08-0 (generic)	---	0			preReg									
PEG-4 Cocamide	----	---	0			0									
PEG-5 Cocamide	61791-08-0 (generic)	---	0			preReg									
PEG-6 Cocamide	61791-08-0 (generic)	---	0			preReg									
PEG-7 Cocamide	61791-08-0 (generic)	---	0			preReg									
PEG-11 Cocamide	61791-08-0 (generic)	---	0			preReg									
PEG-20 Cocamide	61791-08-0 (generic)	---	0			preReg									
PEG-3 Cocamide DEA	----	---	0			0									
PEG-20 Cocamide MEA	----	---	0			0									
PEG-6 Hydrogenated Palmamide	----	---	0			0									
PEG-50 Hydrogenated Palmamide	----	---	0			0									
PEG-13 Hydrogenated Tallow Amide	68783-22-2 (generic)	---	0			0									
PEG-2 Tallowamide DEA	---	---	0			0									
PEG-5 Lanolinamide	----	---	0			0									
PEG-2 Lauramide	----	---	0												
PEG-3 Lauramide	26635-75-6 (generic)	---	0/8			0									
PEG-5 Lauramide	26635-75-6 (generic)	---	0/8			0									
PEG-6 Lauramide	26635-75-6 (generic)	---	0/8			0									
PEG-11 Lauramide	----	---	0			0									
PEG-3 Oleamide	----	---	0			0									
PEG-4 Oleamide	----	---	0			0									
PEG-5 Oleamide	----	---	0			0									
PEG-6 Oleamide	----	---	0			0									
PEG-7 Oleamide	----	---	0			0									
PEG-9 Oleamide	----	---	0			0									
PEG-4 Rapeseedamide		√	0			0				X					
PEG-4 Stearamide	----	---	0			0									
PEG-10 Stearamide	----	---	0			0									
PEG-15 Stearamide	----	---	0			0									
PEG-50 Stearamide	----	---	0			0									
PEG-5 Tallow Amide	8051-61-4	---	deltd #			0									
PEG-8 Tallow Amide	----	---				0									
PEG-50 Tallow Amide	8051-63-6	---	deltd #			0									
PEG-2 Tallowamide DEA	----	---	0			0									
Polyglyceryl-4-PEG-2 Cocamide	----	---	0			0									
PPG-2 Cocamide	----	---	0			0									
PPG-1 Hydroxyethyl Caprylamide	----	---	0			0									
PPG-2 Hydroxyethyl Cocamide	201363-52-2	√	0			CLP				X					

Ingredient	CAS #	InfoB	SciFin	FDA	EU	ECHA	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH
PPG-2 Hydroxyethyl Coco/Isostearamide	----	√	0			preReg				X					
PPG-3 Hydroxyethyl Soyamide	----	---	0			0									
PEG-9 Cocamide MEA	***Not INCI***			***VCRP***		***0***									

Search Strategy

PubMed (8/28/17; weekly updates are received):
(61791-08-0[EC/RN Number]) OR (68783-22-2[EC/RN Number]) OR (26635-75-6[EC/RN Number]) OR (8051-61-4[EC/RN Number]) OR (8051-63-6[EC/RN Number]) OR (201363-52-2[EC/RN Number]) – 0 hits

(alkoxylated AND amide) OR ((PEG or polyethylene glycol) AND (cocamide OR palmamide OR lanolinamide OR lauramide OR oleamide OR ricinoleamide OR rapeseedamide OR stearamide OR tallowamide OR (tallow AND amide))) OR ((PPG OR polypropylene glycol) AND (cocamide OR caprylamide OR isostearamide or soyamide)) - 14 hits/1 useful

SciFinder (8/28/17; weekly updates are received)
CAS #s – see table
by name – 0 hits
structure search (per Bart) – 6056 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)
- Scifinder (https://scifinder.cas.org/scifinder)

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

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org - can be used as a first check for information sources/CFR citations/etc (searched 8/29/17)

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

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

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

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

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

ALKOXYLATED FATTYAMIDES

FULL PANEL – DECEMBER 4, 2018

DR. MARKS: These 40 ingredients were first reviewed in September of this year and an insufficient data announcement was concluded. Method of manufacture was in need, impurities data, dermal absorption on two ingredients and, if absorbed, dermal tox data. Our team felt we could move forward now. We did get some data. We actually felt comfortable in September, So, our team moves a tentative report be issued with a safe conclusion. And I can do discussion in a minute if you want.

DR. BERGFELD: Okay. Don, do you want to second that make another comment?

DR. BELSITO: Partially second it, safe when formulated to be non-irritating. Ethanolamides and diethanolamides, in the discussion, should not be used in cosmetic products wherein which N-nitroso compounds can be formed. Also in the discussion, free DEA in diethanolamides do not exceed the present practice of use in concentration of DEA itself. For the conclusion, safe as used when formulated to be non-irritating.

DR. BERGFELD: Acceptable?

DR. MARKS: That's fine.

DR. BERGFELD: Any other --

DR. MARKS: We have different sensitivity to irritants, I can see, today.

DR. BERGFELD: Any other discussion points or editorials?

DR. MARKS: Yeah. We felt that because of the memo from yesterday, so a late-breaking Wave 4, maybe that was; that there should be a risk assessment section in the document to address that memo from yesterday. That also included a reference. And we really wanted to capture the reference and, at least, the precedent, or the tradition, is we don't include references in the discussion, or else we would have the risk assessment in the discussion. So a new section, risk assessment section. And then also in the discussion, that the 28-day oral tox, the DART, and that the use concentrations are not high in cosmetics, reaffirm the safety of these ingredients.

DR. BELSITO: I'm not sure the risk assessment that you're requesting.

DR. HILL: It's in that thing we got yesterday, the exposure assessment -- I'm sorry. I figured you can hear me. I'm pretty loud. What's in the letter that we got yesterday, the exposure assessment alkoxylated fatty amides. It was important because we'd asked questions about the low molecular weight, the PPG2 hydroxyethyl cocamide was one of them that's looked at in here. And also the PEG-4 Rapeseedamide, where we might have some low molecular weight fatty acids attached to a small PEG group.

There was an exposure calculation done, and it's a pretty nice analysis. And it's just a margin of exposure, that's all that's there. But we thought that information could be rolled into the report.

Then we talked about just distilling it down to a sentence, or three, in the discussion. Then the references can't be included. And I made the comment that I don't know why we don't include references in discussion; that every journal, I'd ever published in, uses references in discussion if you need it. But, apparently, we have a prohibition, so then where else do we put it?

DR. BELSITO: I mean, I just assumed that this would be added to the report.

DR. MARKS: Okay, all right.

DR. BELSITO: Are you asking that CIR do another separate risk assessment?

DR. MARKS: No, not at all.

DR. BELSITO: Okay. So, this is just being added to the report. This is information we got.

DR. MARKS: We were specific of where it would be added to the report, in another section.

DR. BELSITO: I see. Okay. Just two other things in the discussion, pesticide and heavy metal boilerplate.

DR. KLAASSEN: So where did you conclude that this risk assessment should be placed?

DR. MARKS: We felt it actually have a risk assessment section before the discussion; since, again -- and, Ron, I like your comment. I'm not sure -- Bart, maybe you can answer it, or anybody else, why we don't allow references in the discussion? Because this could be handled in the discussion, if we allowed references. We don't want to put this in the document without having it referenced.

DR. HELDRETH: Classically, our report structure has been that the summary section, and the discussion sections, are pulling everything together from what's previously in the report. So, it's not so much a limitation on not having references in the discussion section, it's we shouldn't be bringing something up for the first time in the discussion section. It should be in the body of the report. That's our report structure that the panel has set up.

DR. HILL: It's something that I had to work hard to learn to write is, that you have results in the results section and then you discuss them in the discussion section. And in the discussion, if you need to add in things from the literature, related to the results, that's where those go.

DR. BELSITO: Right.

DR. HILL: And I thought, well, in the particular case, you could distill down what's two pages, in here, to about three or four sentences that would capture the information. But if we had to exclude the reference, we would lose that piece. So, then we created a risk assessment and put more of it in, which is fine with me.

DR. BERGFELD: Other comments? Is there a vote against the risk assessment, a new category in the document? No. Okay.

DR. LIEBLER: Just pop it in before the summary.

DR. BERGFELD: Before the summary. Okay. All right. Then Dr. Marks has proposed safe, and had added on to that, by Dr. Belsito, non-sensitizing?

DR. MARKS: Non-irritating.

DR. BERGFELD: Non-irritating. I wrote down sensitizing. All right. I'll call the question. Safe and non-irritating? Approved. Unanimously.

Belsito Team – December 3, 2018

DR. BELSITO: Okay, alkoxylated fatty amides, we had an exposure assessment that was sent out today. We looked at 40 ingredients in September of 2018. And at that meeting there was 41, but we dropped one, there was a tertiary amide. So, now we're looking at 40.

And at that point, we went insufficient for method of manufacturing, impurities and dermal absorption of PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide. And if they were absorbed, we're asking for 28-day dermal or some other method of assessment, absorption through skin, before looking at other tox endpoints.

We have some data. We didn't get all of it. But I thought we got enough, personally, to go formulated to be non-irritating with the ethanolamides and diethanolamides, not to be used in cosmetics in which *N*-nitroso compounds could be formed. And with a restriction on free DEA and diethanolamides, not to exceed the present practices of use.

And so, that's where I came out on this. And just wondering where you folks did. And then a few other comments along the way.

DR. SNYDER: I agree. In reviewing the data, we had a pretty nice developmental reproductive toxicity study that had a very large NOAEL. So, I don't think we're worried about systemic toxicity, so I don't think we need to request the 28 day any longer. I agree. We received some impurities and method of manufacturer so, as far as I was concerned, the data needs have been met.

DR. LIEBLER: I felt the same way. I have a note here to ask Paul for his opinion, which we just heard. But I could go without the 28-day dermal tox, given that the acute dermal LD50 is so high. Short term oral showed little evidence of tox and then of course there's the repro that Paul just cited. So, I think we're clear on everything.

DR. KLAASSEN: I agree.

DR. BELSITO: In the discussion we'll need the pesticide and heavy-metal boilerplate. And then for the inhalation, I mean, it's sort of bad that we're not doing this first. So, how are we going to handle now, with the new data, the use in deodorants and antiperspirants? Because our boilerplate doesn't deal with those at all, they deal just with sprays and pumps.

MS. FIUME: We do actually have separate language when something is used in a deodorant.

DR. BELSITO: Okay. But when I was looking at the tables, I didn't see any DOAP list, it was just possible inhalation aerosol. So, how do we know whether they are or are not used in a deodorant, or an antiperspirant that's a spray? Because it just say, you know -- oh, there is an underarm deodorant. Yeah, okay. Sorry.

MS. FIUME: If it's just VCRP data, we didn't give the indication for deodorant. Because antiperspirant is an OTC, so we don't handle antiperspirants. But for the deodorant we will say, may be used in sprays, but we don't know. And then when we receive concentration of use data, from industry, they will normally indicate whether or not it's a spray if they have that information. And then we bring that into the report.

DR. BELSITO: Okay. So, then the assumption always is if we have a couple of ingredients in the group that are not used in deodorants, that all of the others would also not be used in deodorants.

MS. FIUME: That's correct. Because we try and say as used in the report.

DR. BELSITO: Okay.

DR. BERGFELD: So, what is your discussion going to contain?

DR. BELSITO: Well, I think the discussion is going to contain that, you know, we do have data. As Paul said, the good DART data on the --

DR. SNYDER: As well as the systemic toxicity.

DR. BELSITO: Right. Across the board. The Rapeseedamide that we have the DART data on. And so, I think, from my standpoint that's also one of the smaller ones, we can sort of read across from that. We have lots of data on PPG and PEGs. I mean, I just think that there was low systemic toxicity. The big issue here is irritation. And then the new potential for -- you know, since there are plant sources, pesticides and heavy metals.

MS. FIUME: Then in addition to what is in the draft discussion, bring in why systemic toxicities isn't a concern. Bring in our language about it possibly being irritating, so that's a caveat. With the discussion that's there, the draft, is there anything that you want out of that draft, or anything else added to that draft language?

DR. BELSITO: In the draft -- I'm trying to remember, I did this early -- you mentioned about limiting DEA and diethanolamides not to exceed present practice of use and concentration for DEA itself. And you mentioned not to formulate in which *N*-nitroso compounds could be formed. Is that correct?

MS. FIUME: Yes on the *N*-nitroso compounds. I believe I need to add language specific to -- no. The DEA language is there as well. And the heavy metal and impurities language is also there.

DR. BELSITO: Yeah, I thought you had it all.

DR. KLAASSEN: I thought in the draft discussion, in the second paragraph there, the third line where it says could be obtained by read across to the entire group. So, in this group, per se, we don't have any information on dermal absorption. So I think what you need to add in there is that you're using other compounds, like this PEG-2 Hydroxyethyl Isostearamide to kind of come to that conclusion, which isn't really a part of this group per se. Just so it's clear to the reader.

DR. BELSITO: Any other points for the discussion?

DR. LIEBLER: This isn't for the discussion, but it's under impurities, and it's just a little thing I thought could be confusing to the reader. It actually came up in the discussion last time, in our transcript I was looking at. At the bottom of PDF 21, under impurities for the PEG-4 Rapeseedamide, it says, "according to another source PEG-4 Rapeseedamide (as the raw material) is reported to be 60 to 80 percent pure." Now, if that means up to 40 percent impurities, or is that simply active matter? If it's the latter, it shouldn't be represented as an impurity.

MS. FIUME: I will double check it.

DR. LIEBLER: Okay.

MS. FIUME: I want to say it says 60 to 80 percent pure, and not active ingredient; because I think I would have used the term active ingredient.

DR. LIEBLER: Right.

MS. FIUME: But I will doublecheck.

DR. LIEBLER: And in that case, it sort of lazy, careless wording on the part of whoever prepared that sheet; but it's really, really misleading. And if it's possible to clarify that, it would be very good for us to do that.

DR. EISENMANN: It came from the NICNAS summary I believe. And that's just how they report things sometimes. And it probably is -- because it's a surfactant, it's probably sold as 60 to 80 percent.

DR. LIEBLER: Right. That's what I would figure, too, based on the chemical class, but it's just -- anyway, it might be worth taking one more peek. And if we can't resolve it, I guess we leave it. But it's not a big deal, but I just want to make sure we're kind of clear on that.

DR. BELSITO: Anything else?

Marks Team – December 3, 2018

DR. MARKS: Okay, let's move on to the alkoxylated fatty amides. And we also received some data this morning, December 3rd memo, from the Science and Support Committee about the NOELs of the PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide. Ron, Ron and Tom, I don't know, have you read this from this morning?

DR. SHANK: That was sent to us by email, wasn't it?

DR. MARKS: No.

MS. FIUME: Carol handed it out this morning.

DR. MARKS: It was handed out this morning. Here. If you don't have it, Ron, here you go.

DR. SHANK: Well, it must be here.

DR. MARKS: I think we need to be sure we've looked at this before we move on. And then there is a Wave 3 --

DR. HILL: What was in Wave 3?

DR. SHANK: Brown algae.

DR. MARKS: So, while you're looking at that, this is a draft tentative report. The panel first reviewed -- here you go, Ron. I actually have your name on it because I wanted your comments.

DR. SHANK: No. I didn't see it.

DR. MARKS: We'll take a minute. I'll just frame it here, Ron.

DR. HILL: And this is actually in Wave 3.

DR. MARKS: It is in Wave 3?

DR. HILL: It is in Wave 3.

MS. FIUME: The data are, but not the Science and Support Committee comments.

DR. HILL: Oh, okay. Where are the comments?

MS. FIUME: They were distributed this morning.

DR. HILL: Okay, then I'm looking at the wrong thing.

DR. MARKS: Yup.

DR. HILL: Yeah, okay. I see it.

DR. MARKS: It's the one dated December 3rd I believe.

DR. HILL: December 3rd, yup. Okay.

DR. SHANK: That's today.

DR. MARKS: That's why it came today.

MS. FIUME: We tried to get it last week.

DR. MARKS: Because I think it's really important since the council, in the memo, addresses the PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide.

DR. HILL: Yeah, this is good info.

DR. SHANK: Basically, that's what I have in my own notes.

DR. MARKS: Good. So, Tom and Ron Hill? I'll let you keep reading, Ron Hill.

DR. HILL: Thank you.

DR. MARKS: So, kind of put it in perspective -- shall I talk or let you keep reading?

DR. HILL: You can talk, yeah.

DR. MARKS: Okay. The panel first reviewed this group of 40 ingredients at the September meeting. And actually, when you read the minutes, our team felt that we could move forward with a safe conclusion. But the Belsito team preferred having an insufficient data announcement, with the needs mentioned below. Method of manufacture, impurities data, dermal absorption on the PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide. We received data, including what we have this morning --

DR. HILL: I did flag the PEG-4 Rapeseedamide, which I didn't look back at the transcript, but I presume that I flagged that when they pointed that out. So yeah, this addresses it nicely, though, I think.

DR. MARKS: So, can we move forward with a tentative report with safe with the new data we have? Particularly, since it adds to what we had -- we had a safe conclusion prior anyway.

DR. SHANK: That's right. Basically, what I've written here is what they said there. Not in so many words, but. We have all 28-day toxicity for both the rapeseed and the hydroxyethyl. We have developmental and reproductive toxicity, oral. And that shows there's no problem. And the oral would give a much higher blood concentration than topical application. The use concentrations are not high. So the concentrations in cosmetics would not be expected to produce blood concentrations greater than those produced in 28-day oral and the oral DART. So, we can remove that request for more data. I would say safe.

DR. MARKS: Safe as used.

DR. SLAGA: Safe as used.

DR. HILL: Yes. I concur.

DR. MARKS: Okay.

MS. FIUME: Can I ask a question? So what they're recommending, to be included in the report, is a risk assessment. And the reason that wasn't in the report is we don't typically include risk assessments unless there is reason to. So, Dr. Shank, with everything that you've gone through, can I just use that in the discussion as opposed to adding a risk assessment section to the report?

DR. SHANK: I don't think risk assessment is at all necessary.

MS. FIUME: Okay. Because that's what this information was -- identified as in the last report.

DR. SHANK: Yeah. But their reasons are that the oral data are perfectly sufficient. We don't need a risk assessment.

MS. FIUME: Great. Thank you.

DR. MARKS: Okay.

DR. HILL: Well, again, I always raise the issue of oral exposure is not dermal exposure, but if you're giving high enough doses, orally, to saturate it within a site, then that's a good -- particularly when it involves rodents, which are more aggressive first-pass metabolizers than humans by a long shot.

DR. MARKS: Okay. I think Ron Shank's addressed that with a 28-day oral tox and the DART.

DR. HILL: Yeah.

DR. SHANK: And the DART.

DR. MARKS: And that the use concentration is not high from cosmetic exposure.

DR. HILL: These are high concentrations in the oral studies, high amounts.

DR. MARKS: Yeah.

MS. FIUME: And I will correct that the actual leave-on dermal exposure is no longer 3 percent. It's 0.35 percent, so it's even lower.

DR. MARKS: Yeah.

DR. HILL: Which one? Rapeseedamide or the other one? The PPG-2 was low in the first place -- Hydroxyethyl cocamide was low in the first place.

MS. FIUME: Was that the one that was 3?

DR. HILL: It's 0.35. I don't know. But the PEG-4 Rapeseedamide, this looks like up to 8 percent -- 15 percent.

MS. FIUME: But that was rinse off, correct?

DR. HILL: Rinse off.

MS. FIUME: Yeah. The highest leave on is now 0.35 percent, PPG-2 hydroxyethyl cocamide. And that's the highest leave-on percent of any ingredients. It's 0.35, not 3 percent.

DR. MARKS: Yeah, that's much different.

DR. HILL: So we don't have 8 percent PEG-4 Rapeseedamide?

DR. MARKS: Yeah. That's what I had, the PEG-4 Rapeseedamide.

MS. FIUME: So, that's not dermal, that is probably a tonic -- hair tonic.

DR. HILL: Okay. Actually, let's see; makeup remover, shower gel, hand-wash soap, shampoo, hair conditioner. So, the trouble with hair conditioners is always, is it leave on or is it not. Because some are.

DR. MARKS: Okay. I didn't have an alert from the sensitivity issue.

DR. HILL: I don't either.

MS. FIUME: The PEG-4 Rapeseedamide?

DR. HILL: Yeah.

MS. FIUME: There is no leave-on uses of that ingredient.

DR. HILL: Well, it's a hair conditioner in that list. I'm looking at the memo from Science and Support Community.

DR. MARKS: And the other one was 0. --

MS. FIUME: 0.35.

DR. SHANK: But aren't they rinsed off?

DR. HILL: No. There are leave-on hair conditioners. And unless it says so, you don't know.

DR. SHANK: Leave on?

DR. HILL: Yup.

DR. SHANK: Put it on and leave it? Really?

MS. FIUME: Yeah. I mean, we generally consider them to be rinse off. But the difference would be they're not a dermal exposure.

DR. HILL: They are if they're a leave-on hair conditioner.

MS. FIUME: Well, it would be a conditioner, but generally if you're leaving a conditioner on, you're not going to want to -- speaking if I were to use it, I would not want it on my roots. Because then it's going to weigh down your hair and make it greasy. So it's typically on the ends.

DR. HILL: Yes. But the use patterns where I live are substantially different than that. And then I think about those people that are using that, and then commonly they're employed in things like in the back room of restaurants where they have hair caps on. And they do leave things on, and they leave them on for several days between washings, because, again, pattern of use.

So, if you don't know one way or another, I think you always have to entertain the notion, with a conditioner, that it could be. Unless you know otherwise.

DR. MARKS: So, are we concerned with the PEG-4 Rapeseedamide, from a systemic point of view, for that concentration? We aren't from a contact dermatitis point of view. And I think based on what Ron Shank said --

DR. SHANK: Well we have oral and DART; 28-day oral for Rapeseedamide. And DART for rapeseedamide.

DR. HILL: I'm not concerned. But I like his analysis because if is 8 percent in a leave-on conditioner, and scalp is reasonably penetrable skin, then you're still covered.

DR. MARKS: Okay.

DR. HILL: The question is, do you include this in any manner in the document?

MS. FIUME: I thought I heard no, because it was presented as a risk assessment.

DR. HILL: And what, I guess, I'm saying is we went through all the trouble of doing this, why would you not?

DR. SHANK: Why would you not what?

DR. HILL: Put it in. I flagged the question for Rapeseedamide because we have a distribution of molecular weights that are less than 600, and physical chemical properties that suggest dermal absorption would be pretty good. We didn't have data to say otherwise either. That was flagged the last time. So I wasn't good with safe as used, really.

DR. MARKS: But now you are?

DR. HILL: Because I like this.

DR. MARKS: Okay.

DR. HILL: Which shows we have a good comfortable margin.

DR. MARKS: Well, that's a little different. You were talking about convert. Is there any reason, Ron Shank, you feel that shouldn't be included as a more expanded discussion?

DR. SHANK: That's all right. But to go and do risk assessment, I don't think it's necessary.

DR. MARKS: Yeah. Okay. I think that's the difference in what you were asking, do you need to do more than what's on there.

MS. FIUME: No. I was asking if you wanted -- what they presented is a risk assessment, from a different source, from the Australian source. If you wanted the risk assessment in the report. And the reason I didn't include it, the first time, is because the panel has been on record saying that we don't want a risk assessment in every document.

DR. MARKS: Right.

MS. FIUME: So, that's why I didn't bring a risk assessment in.

DR. MARKS: Right.

MS. FIUME: And that's why I was confirming whether or not you wanted a risk assessment section in the report, or just what Dr. Shank gave us for the discussion.

DR. SHANK: Oh, I see. I thought you meant we do a risk assessment.

MS. FIUME: Oh, no, no, no.

DR. HILL: Well you can just capture it as a MOE, as a margin of exposure assessment, right. I mean, it wouldn't have to be a risk assessment --

DR. MARKS: Well, either that, or does it need a whole separate section, or just put in the discussion?

DR. SHANK: You can refer to it.

DR. MARKS: Yeah.

DR. SHANK: To the Australian.

MS. FIUME: But I can't, in the discussion, if the information's not in the report; because I can't reference the discussion.

DR. SHANK: I don't think we need it.

DR. MARKS: That old conundrum of no reference -- you don't think we need it. I know you'd already -- Ron Hill, you feel more comfortable with it. And then where would you put it?

DR. SLAGA: I don't think we need it either.

DR. SHANK: Well, then you'd have to add a new section, risk assessment.

DR. HILL: You could probably condense the salient information, in all of this, in terms of margin of exposure into one sentence in the discussion. But if you can't put references in the discussion, which again I totally don't understand, then I'm not sure where else you put it.

DR. MARKS: Okay. So, let's condense it as you suggest. Basically, what you've summarized already, Ron, from the last meeting's comments in the minutes. Let's deal with it that way.

DR. SHANK: Do we add a section, risk assessment, and then refer to the Australian document? Is that published in a peer review journal?

MS. FIUME: The NICNAS document is referred to in the report, and a lot of this information is pulled out of it. But the risk assessments, itself, is not included in our CIR assessment.

DR. HILL: Our formatting doesn't have an allowance for exposure assessment, and is really not ADME per se. But we do have sometimes where we say, in the absence of direct data, under the ADME section somewhere to make it exposure. I realize I'm suggesting something that's a little off of our usual pattern.

And then, like I said, you probably could include the salient information here in less than two or three sentences, and maybe one long one. I don't know, but obviously they were a little concerned. But I was specifically concerned because of the low molecular weight and physical chemical properties that we get so sensitive to.

MS. FIUME: The log K_{oWs} are in the properties table.

DR. HILL: Yeah, I know.

MS. FIUME: I think that's the information that they used to develop these numbers, were the log K_{ows}.

DR. HILL: Yeah. And so my point is, here it shows the log K_{ows} put us in a range where that could be a concern. And what this shows is our dermal exposure, by any (inaudible) would be far lower than what we're covered by with our oral dosing studies. And maybe that's all that needs to be said. And I would think it could go in the discussion with a reference to the NICNAS, if we could put a reference in the discussion section.

DR. SHANK: Well, you can't, so.

DR. HILL: And apparently we can't.

DR. SHANK: Well, if it's out there, I guess the report should refer to it.

DR. MARKS: Mm-hmm.

DR. SHANK: It's just supports what we've been saying.

DR. MARKS: Exactly. And we're actually stalled, so to speak, over how we incorporate this information in the report. And so, I think if it requires a risk assessment title, would you put it under that?

DR. SHANK: Yes. If we put it in the report.

DR. MARKS: Yes.

DR. SHANK: It will have to go in the section called Risk Assessment.

DR. HILL: And where does that fall in our flow?

DR. SHANK: Near the end.

DR. MARKS: Yeah.

MS. FIUME: Typically, we state that it goes in whatever section it's appropriate to.

DR. SHANK: It's not a separate -- like carcinogenicity?

MS. FIUME: When we first did it, we had it separately. And then I think the wording was, Risk Assessment will go under whichever section it falls with. Because it could be looked at from different aspects.

DR. HILL: So, for me that's absorption under ADME. Even though we have no direct data, and in the absence of direct data, it would be an exposure.

MS. FIUME: Typically it has gone under the human irritations -- or no, under clinical assessment, I believe. I don't know we've had it under ADME before.

DR. HILL: Well, talk it over. But to me, that's where it would go. It's just how much could potentially get into the system conservatively. We're in good shape there.

DR. MARKS: So, basically, I think, what we're going to say, is we'll create a new section in this report, a Risk Assessment, and that will include the information from your December 3rd memo. From the Science and Support Committee, referring to the Australian National Industrial Chemicals Notification Assessment Scheme. You can decide where to put it. It has to be a separate section. I don't think it matters whether it's two sections before the discussion or whatever. Does that sound reasonable?

DR. SHANK: I would put it separate because everyplace else you have hard data.

DR. MARKS: Yeah. That's what I mean, separate. Right.

DR. SHANK: And a risk assessment is not hard data.

DR. MARKS: Mm-hmm. But it's all based on the council's December 3rd memo.

DR. SHANK: Yes.

DR. MARKS: Yeah. So, I think we agree that we create a risk assessment section that covers the December 3rd memo. And that way, Ron Hill, we don't have to try and distill this into one or two sentences to catch the -- it could still be done in the discussion, but now we have the reference.

DR. HILL: Great.

MS. FIUME: And then can I ask, was it safe or safe when non-irritating?

DR. MARKS: I have just safe. And I didn't have any notes in terms of -- let me go back to the original, if there was any issues with irritation or sensitization.

DR. SLAGA: No. Not in the initial.

DR. MARKS: Formulated to be non -- yeah, I can see where -- no. I don't have that in there. Yeah, okay. So, just safe.

MS. FIUME: All right, thank you.

DR. MARKS: Okay. So, tomorrow, I'm going to move that our team recommends issuing a tentative report with a safe conclusion for these 40 ingredients. We're going to create a risk assessment section, which will cover the December 3rd

memo, with the references, from the council in the discussion. Discusses the 28-day oral tox, the DART and the use concentration is not high in cosmetic ingredients. Does that capture your thoughts?

DR. SHANK: It does.

DR. MARKS: Okay.

Full Panel – September 25, 2018

DR. BELSITO: This is the first time that we're looking at the safety assessment of 41 structurally-related alkoxylated simple amides. A few of these ingredients are dye, and then alkoxyl substituted amides. But most of them are fatty amides or mono.

We looked at all of the data. We also received data in Wave 2, regarding information from Council about the fact that there were a number of these ingredients for which there were no suppliers, and took that into account. And came up with a conclusion that these, at this point, were insufficient for manufacturing and impurities.

Dermal absorption, 28-day dermal, and if absorbed, other toxicity endpoints may be necessary. With a caveat that we may be able to read across from the two that are most frequently used. The PPG-2 hydroxyethyl cocamide in 342 formulations, and the PEG-4 Rapeseedamide in 280. So, basically using those as read-across and then potentially for the others, and getting information on manufacturing, impurities, dermal absorption, 28-day dermal.

DR. BERGFELD: So, in essence you're going insufficient. You have two lead ingredients that will read across to the others.

DR. BELSITO: Potentially.

DR. BERGFELD: Potentially. Is there a second?

DR. MARKS: Our team actually had a conclusion of safe for all 41 ingredients. Ron Shank, do you want to comment why, because a lot of this has to do with, obviously, toxicity, which Don listed.

DR. SHANK: I recommended using PEG-4 Rapeseedamide and PPG-2 hydroxyethyl cocamide for which we have a lot of data to read across to cover all the others, with the possible exception of the two dialkoxyl fatty amides. I need help from the chemist, if those could be included with the read-across or not.

The PEGs and the PPGs and the amides, individually, have already been reviewed and found to be safe. So, using the read-across for those two, the PEG-4 Rapeseedamide and the PPG-2 hydroxyethyl cocamide, to read across. So, they would be safe when formulated to be nonirritating.

DR. BELSITO: What about the lack of manufacturing data information?

DR. MARKS: Ron is smiling because we had this discussion yesterday.

DR. SHANK: We have reviewed a very large number of ingredients on this panel, and very seldom has the need for method of manufacture had a definitive influence on the conclusions made. So, if someone can argue as to why method of manufacture is needed, other than to fill in a blank, I would like to hear it.

DR. BELSITO: Because that would give us some clue as to impurities. Right now, we just know that there is some dioxane in the PEG-4 Rapeseedamide that's one-part per million maximum. And that the rapeseedamide as a raw material is reported to be 60 to 80 percent pure. What is the other 40 to 20 percent of the rapeseedamide?

DR. SHANK: Then ask for impurities, not method and manufacture.

DR. BELSITO: We asked for method and manufacture and impurities. We can always decide not to act on it.

DR. LIEBLER: Once in a while, when someone on our team loses their enthusiasm for box-checking, it's up to the rest of us to step forward and pick up the flag and bear the standard forward. Ron, I'm happy to do that for you. I know you'd do it for me.

But, seriously, I think that at this point there's no reason not to ask. We will probably get sufficient information to satisfy our need to have done the appropriate diligence on that issue. I don't think it's going to be limiting in the final report.

And I do agree with your suggestions on the read-across, use for the two ingredients for which we've got pretty abundant data. I think Don was essentially saying pretty much the same thing. And I have no problem with including this substituted molecule in the assessment.

DR. BERGFELD: Wait, Ron Hill has something.

DR. HILL: I agree with pretty much everything you just said. I was just making note that -- because one of our lead ingredients, the read-across ingredient, was the PEG-4 Rapeseedamide. There is a significant molecular weight, less than 600 fraction, and I was much more interested in getting information about what's in that fraction.

And in our discussion of manufacture, what we really said in this case was we're really interested in potential impurities. And what we think we know, is that the main one that we might encounter is dioxane and we would include our usual limitation on that. But, I do think having a little more idea about what potential impurities might be in these is important as part of due diligence.

DR. MARKS: I think, yeah, it's fine.

DR. BERGFELD: Ron Shank?

DR. SHANK: Yes.

DR. BERGFELD: Any other comments? Tom

DR. SLAGA: No.

DR. BERGFELD: Curt?

DR. MARKS: Second.

DR. BERGFELD: There's a second from Dr. Marks, quickly stated. Okay, you want to restate the motions since we've had some discussion?

DR. BELSITO: Insufficient for method of manufacturing, impurities, 28-day dermal; and depending upon that, other toxicity endpoints for the two lead ones, the PEG-4 Rapeseedamide and the PPG-2 hydroxyethyl cocamide.

DR. BERGFELD: All right, and it's been second. I'm going to call for the vote. All those in favor please indicate by raising your hand. Okay, unanimous.

Belsito Team – September 24, 2018

DR. BELSITO: Alkoxylated Fatty Amines. So, this is the first time we're seeing the safety assessment of 41 alkoxylated fatty amines. A few of these are di-N,N-alkoxyl-substituted amides. Most of these are alkoxylated fatty amides.

DR. LIEBLER: They're all amides.

DR. BELSITO: They're all amides?

DR. LIEBLER: Yup. How are you with the sensitization data?

DR. BELSITO: I don't know, I'm getting there now.

DR. LIEBLER: Okay.

DR. BELSITO: I just ask, can we bring in data from PPG, PEG, Tallow, et cetera documents? Is that needed?

We don't have any method of manufacture. HRIPT is an only 50 for the two with the biggest use, but the guinea pig maximization tests were negative, so I'm okay with sensitization and irritation.

DR. LIEBLER: Okay.

DR. BELSITO: Dioxane impurities, respiratory boilerplate, other. And I wondered whether we're insufficient for manufacturing in 28-day dermal tox, and if absorbed, a 28-day dermal, and if absorbed, other tox endpoints. If so, could we read across from the two most frequently used, which were PEG PPG-2 hydroxyethyl cocamide and PEG-4 Rapeseedamide?

DR. LIEBLER: Yes, so I agree with all of those. I think that we need method of manufacture impurities, so right now we're insufficient for that. We need dermal absorption on a 28-day dermal, and if we had it for those two we would be covered. For those two that you just mentioned, which are the high use ones.

MS. FIUME: Dermal absorption...

DR. LIEBLER: And 28-day dermal tox. We have no carcinogenicity data, but the mutagenicity profile is clean. And these really don't have structural alerts. I'm not really worried about the lack of carcinogenicity. If the other team feels that we need it, I won't argue forcefully at this point; but the question is more tox than carcinogenicity here.

MS. FIUME: Can I ask for a point of clarification on the dermal absorption? Typically, when we have mixtures like this we say it's not feasible because they don't know what they're looking for. Is there an aspect that they would find in the dermal absorption?

DR. LIEBLER: Well, we use that logic for things like botanicals.

MS. FIUME: Okay, but not something like this?

DR. LIEBLER: This is a much more defined mixture with certainly very representative constituents that could be very clearly, easily measured. I think it's fair to ask for that.

MS. FIUME: I just searched the PEG Tallow type ingredients. We have a report on the PEG Tallow amines, but I don't have anything on just PEG Tallow that wouldn't have an amine attached.

DR. LIEBLER: I don't think that helps us.

DR. BELSITO: Let me see what Paul said. "No method of manufacture, impurities for one. The second greatest use with PEG-2 hydroxyethyl cocamide #1. No absorption. Tox data almost entirely for PEG-4 Rapeseedamide." Pretty much what we said.

DR. LIEBLER: I think that's really representative of the class.

DR. BELSITO: "Genotox, no carcinogenicity data."

DR. LIEBLER: Right.

DR. BELSITO: Yeah. So, exactly what we said. "Council comments; 23 of the ingredients have no suppliers." And then he had questions regarding the grouping to you.

DR. LIEBLER: The grouping?

DR. BELSITO: Just reading what he stated.

DR. LIEBLER: I think the only grouping issue is we have a few that are di-N,N-alkoxyl -- a few. And then most of them are mono-N-alkoxyl, and I think they can all be treated together.

DR. ANSELL: We would support dropping the di-substitute at the end in that there is no data on it, and it isn't going to inform the discussion on the other materials.

DR. BELSITO: Which one?

DR. ANSELL: The di-N,N-alkoxyl-substituted amides.

DR. BELSITO: Which ingredients are those?

MS. FIUME: I know two of them are PEG-3 cocamide DEA, and PEG-2 Tallowamide DEA.

DR. BELSITO: You want to drop those? Dan?

DR. LIEBLER: I don't object to dropping them. If you wanted them in the report to be reviewed, because they were in the dictionary then we could treat them. I mean, I don't think that we couldn't deal with them. But if there is a compelling reason, sort of administratively, to drop them, then I have no objection.

MS. FIUME: CIR included them in grouping. So, I know his stand on it would be to keep them; because it's actually mentioned in the introduction that they are different --

DR. LIEBLER: So, Jay, the reasoning for dropping them is that there are no suppliers and we are unlikely to get data?

DR. ANSELL: No, that the mono-substituted and the di-substituted do not inform -- the di-substituted materials do not inform the discussion about the mono-substituted materials. There is no data and it's unlikely, if there were data, that you could rely on it for the mono-substituted materials.

DR. LIEBLER: I don't see that as being a liability for the di-substituted. I think the mono-substituted would inform the evaluation of the di-substituted. If the di-substituted needed to be in the report because they are in the dictionary because CIR wanted them there, then we can review them, it's just going to be insufficient.

We're not counting on the di-substituted, if they are there, to inform the evaluation of the mono-substituted, I think. It would be nice if they did somehow, but we're not in that situation. I don't see it as a reason to eliminate them.

DR. ANSELL: If the only reason is that they are in the dictionary, but they do not help with the safety assessment, then we would argue to drop them. If you think that the di(s) can be supported with the data on the mono, then we can see where that assessment goes. I was thinking the other way around.

DR. LIEBLER: First of all, I don't see any reason why the di(s) should really be different in their toxicity. In our evaluation, I don't see why they should be different. They are similar enough in structure to the other materials that -- I guess the question would be, even if we have no data in uses for the di(s), would we be comfortable in reading across from the data on the mono to support the di(s)?

I would certainly be open to that possibility because of the similarities, the lack of structure alerts for toxicity, etcetera -- for carcinogenicity, and the lack of anything but maybe a little irritation for these in the skin.

DR. ANSELL: Well, this is the first review, so I think we're pretty flexible at this point.

DR. LIEBLER: That's how I feel. And let's see how the discussion with the full panel goes tomorrow. Maybe the other team might have a reason to take a position on that, and we can audible on it.

By the way, just for purposes of understanding this group, I want to just say I like the idea of including these in sort of structural, general formula groups in Table 2. That's a nice touch, I like that.

MS. FIUME: Thank you.

Marks Team – September 24, 2018

DR. MARKS: Okay. Next is the alkoxylated fatty amides. This is a draft report from Monice. This is the first time we've seen these ingredients; therefore, it's a first review. There are 41 ingredients. Tom, Ron and Ron, ingredients okay? And then there was an issue raised in the Wave 2 memo about the dialkyl substituted amides. Am I saying that right, Ron Hill? Amides or amides? Which his better? Or does it matter?

DR. HILL: It doesn't.

DR. MARKS: Good.

DR. HILL: Amides, amides, amides. All of those are heard and are acceptable as far as I understand.

DR. MARKS: Whether or not these should be included in the report comments. Okay. I'll open it up for discussion. First, ingredients?

DR. SHANK: I thought we could use two of the ingredients for read-across for all of the others, and say they're safe when formulated to be nonirritating. The two for read-across would be PEG-4, Rapeseedamides.

DR. HILL: PEG-4, which --

DR. SHANK: PEG-4, Rapeseedamides.

DR. MARKS: Oh, yeah. Okay, that's the one that has a lot of uses.

DR. SHANK: Right. And PPG-2 hydroxyethyl cocamide. We have data for those. We could use those for read across. Possible exception would be the two dialkoxyl fatty amides, which are PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA. There's no toxicology data on those. And I'm not too sure -- I need help from the chemist -- can we read across from all of the others for those dialkoxyl fatty amides.

The PEGs and PPGs and amides have already been reviewed by themselves and found to be safe when formulated to be non-sensitizing.

DR. MARKS: Yeah, based on a QRA

DR. SHANK: Yes. And we could add the nitrosation caveat to these compounds.

DR. MARKS: Ron Hill?

DR. HILL: Yeah, I'm looking. I'm sorry, I'm looking for one particular one that --

DR. MARKS: Do we have the method -- I had noted here, do we have method of manufacturing and impurities on these?

DR. SLAGA: I thought we did.

DR. MARKS: Pardon?

DR. SLAGA: We have that.

DR. MARKS: Okay.

DR. HILL: You do?

DR. MARKS: I had that as a question mark. And I didn't see any -- and it wasn't checked here in our spreadsheet. And when I looked at the report, I think it says -- let me go, which page that is?

MS. FIUME: PDF page 12.

DR. MARKS: Yeah. Method of manufacturing is not discovered, unpublished. I think -- I mean, we don't move forward -- we could aim for a safe, but I don't think we come to a conclusion of safe if we don't have the method of manufacturing. That would be an insufficient data. Impurities we have. The PEG-4 Rapeseedamide. We don't have it for the other lead ingredient that you --

DR. HILL: For that particular one which he proposed to use for read-across -- I'm getting a ringing, sorry because it's aiming toward the speaker. We've got molecular weight 600 indicated. I really wanted a better sense of the molecular weight distribution as focused on the low end with that one.

DR. SHANK: Which one are you talking about?

DR. HILL: Well, the PEG-4 Rapeseedamide, there's a molecular weight of less than 600 fraction that's indicated. I don't know where the percentage is, but I can find it probably in a minute. At that molecular weight range, we would have dermal absorbability, but then, presumably, surfactant character in which case it probably wouldn't get very far.

DR. MARKS: Sensitization data for that is okay just as Ron had mentioned earlier. Irritation sensitization for both those lead ingredients. But I actually -- again going back -- I had the method of manufacturing and impurities would have been an insufficient data announcement. Ron Hill, what more did you want?

DR. HILL: Well, impurities. If we had representative, method of manufacture. I doubt that most of these would vary. There were a couple places, though, were I had some question about what actually I had in terms of chemical.

DR. MARKS: Where do we have the method of manufacture?

DR. HILL: I don't.

DR. MARKS: No. Okay.

DR. HILL: I didn't flag that. I said, if we had it for a couple of representatives we could, surely, I think, use that to read across. Because I doubt they would vary much. I don't have any reason to think so. But there are a few places where I had -- so we've got this PEG-20 Cocamide MEA, which actually is an N, N-dialkyl, best I can tell.

And then the PEG-5 Oleamide Dioleate, I wanted to confirm that that's Dioleate somewhere out there. I don't know where the Dioleate can even be on that PEG-5 Oleamide. Because the only place you could attach one more would be at the very end of the PEG. So, where is the other one? That's weird.

And I would like, if we're going to use the Rapeseedamide to read across, which I think we're talking about to pull over our fatty acids distribution from our vegetable oil's report; and it would be nice if actually we could get a direct supply from the vendor -- if at all possible -- what that fatty acid distribution in that actually is. I mean, it will vary depending on the source surely; and there may be more than one vendor making it. But if we could get something typical, that would help us with the read-across to all these others.

And same with Cocamide; we already have that pretty well characterized, we just need to pull it over from another report. Because we've Cocamide it to death by this point, I think. We've got lots of information about that. We should put it in here, because that helps with how we're reading across.

And everything else, I think, I agree pretty much with Ron Shank. But we've got the cocamide MEA, which I think is an N, N-dialkyl. I don't know that any new issues are created there, honestly.

And Cocamide DEA, I was a little -- I think I wanted to be clear exactly. Because I don't think there's a structure, exactly what that is. I think I know what it is, but think I know is not really good enough.

DR. MARKS: Are we concerned, chemically, with these surfactants like in cocamidopropyl betaine. Is it betaine?

DR. HILL: I think I determined, eventually, that I had been saying that wrong; and it's betaine.

DR. MARKS: Betaine.

DR. HILL: Because of the way that name --

DR. MARKS: At any rate, we were concerned about DMAPA and amidoamine as contaminants. Is that also a concern as an impurity in these surfactants? Because there's a lot of coco in this.

DR. HILL: No. Because that was not where it was coming from.

DR. MARKS: Okay.

DR. HILL: It was coming from the other component.

DR. MARKS: Okay. So, that's not an issue with these?

DR. HILL: It is, as far as I can tell, not an issue.

DR. MARKS: Okay, good. What do you think about tomorrow, insufficient data announcement, method of manufacture? We got to fill something in that blank. Ron, you're not concerned?

DR. SHANK: Well, in the thousands of ingredients we reviewed how often has method of manufacture been a determining factor in our conclusion?

DR. MARKS: I'm kind of remembering back when we did one ingredient and Dan Liebler said, if there's no method of manufacture, we can't move forward. No, I agree with you, Ron. We'll be seconding it. It'll be interesting to see how the Belsito team comes. But you feel comfortable, and I agree; everything else we can just move forward with a tentative report safe. Okay.

DR. HILL: There was another one, too, where I'm not sure I know what it is, which is the PPG-2 Hydroxyethyl coco/Isostearamide. I'm assuming it is the Cocamide where we have the amide made from the isostearyl amine and hydroxyethyl. But these places where the structures aren't clearly defined, we should really try to get it if they're in use. And if not, we can at least retrace the steps on the dictionary work and confirm.

DR. MARKS: And, Ron Shank, I mean, if we aren't worried about amidoamine and DMAPA in these, then we don't even have to have a caveat, and the conclusion formulated to be non-sensitizing.

DR. HILL: We shouldn't need that for these.

DR. SHANK: Correct.

DR. MARKS: Okay. And then, Ron Shank, you had mentioned, I think, two ingredients you were a little bit concerned about whether they should be included. I don't want to overlook those. There wasn't much data on them, and you were wondering whether we should actually include them in the report. Is a lack of data a reason not to include it? That would be more a reason to say they're insufficient, if they're chemically similar and belong in this group.

DR. SHANK: We could say insufficient or use read-across to include them.

DR. MARKS: Right. Exactly.

DR. SHANK: I'd like to hear from Dr. Hill if the read-across from the two I mentioned would include the two dialkoxyl fatty amides.

DR. MARKS: And those two, again, Ron?

DR. SHANK: One is PEG-3 Cocamide DEA.

DR. MARKS: Hold a second. PEG-3.

DR. SHANK: And the other is PEG-2 Tallowamide DEA. And they're slightly different structure.

DR. MARKS: One is the PEG-2 Tallowamide DEA?

DR. SHANK: Yes.

DR. MARKS: Okay.

DR. SHANK: And the other is PEG-3 Cocamide DEA.

DR. MARKS: PEG-3. Why am I not -- okay. PEG-3 Cocamide DEA. Okay. I see them now on the list. Ron Hill, what do you think about those two?

DR. HILL: I mean, we've got quite a few others in here that are N-hydroxyethyl. From that point of view, what we really are doing is -- the DEA is just two hydroxyethyls attached to the nitrogen, nothing else. And then you start PEGylating and you make one of the two chains longer.

I mean, I'm bothered that we don't have data on PEG-3 DEA, or something, PEG-2 Cocamide, or something smaller. Because the ones that we're reading across from our -- well, I say that. PPG-2 Hydroxyethyl Cocamide might cover it. Sorry, I'm thinking out loud which is never good.

DR. BERGFELD: Which one was that? I'm sorry.

DR. HILL: He was asking about the Tallowamide DEA, but we have Cocamide DEA. Again, I mentioned coconut acids, I guess. That will translate to the kind of distribution we see in Cocamide. And I think we have that information directly, anyway, we could pull over. The comparable information about Tallow, which I know we had in vegetable oils report, one of those. And we've got soy here as well.

What do we got? We got soy, Cocamide, Tallowamide. I think that's all the ones that come -- Rapeseedamide, and here's Lanolinamide. So we know what we're doing on the read across, we need that table that has -- it looks like five. Because the rest of them, we know what they are. They're Lauramide, they're Oleamide, they're Stearamide, those.

I think things read across from the PPG to Hydroxyethyl Cocamide. Coconut oil, I think, goes down to C12 with a significant fraction. It's not huge, but it's significant.

DR. MARKS: Okay.

DR. HILL: Oh, palm. I forgot palm too.

DR. MARKS: It looks like -- if I interpreted that correctly -- we will move forward including those ingredients with all the others. And again, presumably I'll be seconding a proposal to issue a tentative report with safe conclusion. Any other comments?

DR. SLAGA: No.

DR. MARKS: Good discussion.

DR. BERGFELD: Can you repeat your final conclusion. Is it safe?

DR. MARKS: Safe. Yes.

DR. BERGFELD: And you're deleting the method of manufacturing?

DR. MARKS: Pardon?

DR. BERGFELD: You're not demanding a method of manufacturing? You're going to mention it's not there, in the discussion.

DR. MARKS: Well, I have a feeling it will be mentioned by the Belsito team. But if it is, then what I may do is ask Ron Shank to express why he doesn't feel the method of manufacturing is necessary. And if Dan Liebler sticks to his guns, we'll have a duel between Ron Shank and Dan Liebler.

DR. SHANK: That'll be fun.

DR. MARKS: It'll be fun is right. It'll be the meeting of the minds. Okay. Let me save this.

MS. FIUME: And what we can do in our post-meeting announcement is, if this does go forward with the tentative, we can mention that method of manufacture would help improve the safety assessment even though it wasn't an official IDA request.

DR. MARKS: Yeah. I like that, Monice, yeah.

DR. SHANK: That's good.

DR. MARKS: Yeah.

DR. KATZ: I have a question before you move on.

DR. MARKS: Sure, Linda.

DR. KATZ: And this is with regards to 1,4-dioxane as an impurity. Is that going to fall into your discussion at all; particularly, with PEG-4, the Rapeseedamide?

DR. HILL: I'm pretty sure we essentially always include dioxane in the discussion with reports that have PPG and PEG. But we've now captured that, and I think we definitely should put it there.

DR. SLAGA: To discuss.

DR. HILL: And I also, just to mention, I dropped some comments, there's some chemistry clean up that's needed in the first section on chemistry. And in particular, exactly how we say we're reading across from amides to amines, which are chemically quite disparate. It needs to be mentioned.

If we're considering them as potential metabolites, on a couple of these, then that's fine. But approving Cocamine has nothing to do with these. I think some of the ones that were mentioned, PEGs Cocamine, we aren't reading those across to the amides. That would be absurd. I just thought I'd mention that.

MS. FIUME: I'm sorry, Dr. Hill, where are the amines mentioned?

DR. HILL: I dropped a comment, it's in the introduction. There just -- the way some of these things are mentioned. And it's editorial really, but I just want to make note. Similar amines in the cosmetic ingredient review PEGs Cocamine report -- that shouldn't read across. We wouldn't use it to read across to these amides.

And I think they wouldn't be formed as metabolites in this particular case, because on the other end we don't have the coconut acids amines.

MR. GREMILLION: The method of manufacture doesn't inform impurities? I guess, what's the rationale behind method of manufacture in conventional sense?

DR. HILL: I like to see one or the other. And usually, I'm more interested in impurities that might carry over from method of manufacture than the method of manufacture itself. I mean, for me, an insufficiency is impurities. But the problem is the two ingredients that we have -- well, I don't know what the problem is. I don't know if there's a problem with impurities.

DR. MARKS: There wasn't, I think, in the -- we have the impurities --

DR. HILL: That's why I asked for more information.

DR. MARKS: Rapeseedamide.

DR. HILL: Because I was wanting more about the molecular weight, less than 600 fraction, which would include impurities that would concern us.

DR. MARKS: I guess I wasn't concerned with the molecular weight since we had irritation sensitization data which was okay.

DR. HILL: Yeah, but again, if you have something molecular weight, less than 600, at a higher percentage -- I don't know that a percentage was listed here. It could be carcinogenic, just hypothetically, to make sure that people are interested enough. Then, you know, if we get the information.

DR. MARKS: Yeah. Tom didn't have a concern about that. I think it gets back --

DR. SLAGA: I didn't. No. The impurity would take tremendous amount to be carcinogenic. I mean, you're not going to reach that level --

DR. MARKS: I think we're going to have that discussion tomorrow about method of manufacture impurities. And I think you bring up a point. You can see there's a bit of -- how do I want to say -- different opinions among the team members here.

DR. HILL: But I think you're focused on systemic carcinogenicity. I mean, the skin can get cancer, you know. I think you can't totally forget about that idea.

DR. MARKS: Did you want to say anything more tom?

DR. SLAGA: It's a concentration effect. I mean, we would never reach that.

DR. MARKS: Okay.

DR. HILL: Well, what levels are these used? If they're all in rinse off, I agree with you, if they're 90 percent; so, we need to look at that again.

DR. MARKS: The top percentage leave-on on the Rapeseedamide is 9.3 percent.

DR. HILL: Ten percent. So, if you had a one percent impurity of something that's significant, yeah it would only be -- it'd be a modest amount. But it depends on what it is.

DR. MARKS: Okay. I think we didn't answer your question, exactly. We will -- as you can see, when I initially started I was -- we need the method of manufacture. But I think Ron Shank, at least, and Tom agreed, and I'll defer.

And we'll see what the -- that's one of the, how do I want to say, brilliance of the way this panel is set up, is we have two different teams. Which tomorrow, without knowing what the other team has said, we'll come to a conclusion. So, we'll see. I would be surprised tomorrow they move that an insufficient data announcement is made for method of manufacture. And if that's the case, we will concur with that.

DR. HILL: And again, I'm much less interested in the method of manufacture, other than what might carry over versus impurities in a finished product.

DR. MARKS: Yeah. Versus the impurities. And then Monice has had a very diplomatic way to address it; is we'll ask for it no matter what. But it may not be hinging on whether or not a tentative report is issued.

MR. GREMILLION: But the response to your request seems like it may be different, depending on what conclusion you raise.

DR. MARKS: Oh, absolutely. No question. If we move forward with a safe conclusion, it's not a binding request. You're absolutely right.

Okay. Well, we'll see how that works tomorrow. And the other thing, which is always good about the process, is this is a tentative report. We have another look at it before it goes to final. We sometimes change our minds, going from the tentative to the final and ask for more data.

Okay. That's a robust discussion. Yes, next?

DR. HILL: Just because I a little bit overstated my case, there are times where method of manufacture is important. For example, if an enzyme gets used in the process, then how do you get rid of that, if the thing's used in leave-on in mucus membranes.

DR. MARKS: Well, the other example of that is benzene --

DR. HILL: Exactly. And dioxane.

DR. MARKS: -- and the polymers we just discussed. And that was in the conclusion of benzene. It should be. So, Ron Hill, we get that caveat. Yes, the method of manufacturing is important as is impurities. Okay, they both add important data points.

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Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics

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ABSTRACT

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

INTRODUCTION

This assessment reviews the safety of 40 alkoxylated fatty amides, listed below, as used in cosmetics. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all but a few of these ingredients are reported to function in cosmetics as a surfactant – emulsifying agent (Table 1).[1]

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

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

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

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

Much of the data included in this safety assessment were obtained from Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) assessments.[7-9] These data summaries are available on the NICNAS website, and when deemed appropriate, information from the summaries has been included in this report.

CHEMISTRY

Definition and Structure

The definitions and structures of the alkoxylated fatty amides included in this review are provided in Table 1. Provided in Table 2 are the total fatty acid compositions of relevant plant-derived fatty acid oils,[10-12] and of lanolin[13] and tallow.[14]

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

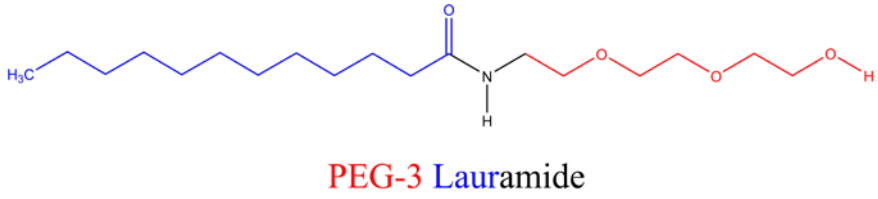


Figure 1. Example of a fatty acid amide, and its mono-alkoxylated surfactant structure

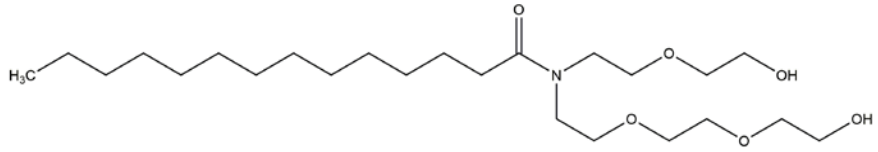


Figure 2. Example of a fatty acid amide (lauramide), and its di-alkoxylated (PEG-3 DEA) surfactant structure (PEG-3 Cocamide DEA is a mixture of fatty acid amides, but the highest concentration constituent therein is the lauramide).

Physical and Chemical Properties

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

Method of Manufacture

PEG-50 Hydrogenated Palmamide

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

PPG-2 Cocamide

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

PPG-2 Hydroxyethyl Coco/Isostearamide

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

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

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

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

Impurities

PEG-50 Hydrogenated Palmamide

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

PEG-4 Rapeseedamide

A supplier reports that PEG-4 Rapeseedamide is 92 - 93% "active matter.[17] Specifications for the presence of 1,4-dioxane are 1 ppm maximum, and specifications for free amides and free amines are 1.64 – 1.75 mv/g and 0.11 – 0.23 mg/g, respectively.[21] According to a NICNAS assessment, the "degree of purity" of PEG-4 Rapeseedamide (as the raw material) is reported to be 60 - 80%.[8] Low levels of 1,4-dioxane, "down to 100 mg/kg or 100 mg/l," may be present. Other possible impurities were not specified, but based on the structure, "it is not expected to contain hazardous nitrosamine impurities."

PPG-2 Hydroxyethyl Cocamide

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

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this safety assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. VCRP data obtained from the FDA in 2019,[23] and data received in response to a Council survey of the maximum reported use concentration by category conducted in 2015,[24] indicate that 12 of the 40 ingredients included in this safety assessment are used in cosmetic formulations.

According to 2019 VCRP survey data, PPG-2 Hydroxyethyl Cocamide is reported to be used in 354 formulations, and PEG-4 Rapeseedamide is reported to be used in 301 formulations (Table 4).[23] All other in-use ingredients are reported to be used in less than 30 formulations. The results of the concentration of use surveys conducted by the Council indicate PEG-4 Rapeseedamide has the highest concentration of use, at 9.3% in hair dyes and colors.[24,25] The ingredient with the next highest reported concentration of use is PPG-2 Hydroxyethyl Cocamide; it is used at 7.5% in "other" non-coloring hair preparations.

The alkoxylated fatty amides are primarily used in rinse-off formulations, with few uses reported in leave-on formulations. Most of the reported uses are in some type of hair or cleansing formulation. However, there are some uses that result in leave-on dermal exposure; the highest concentration of use reported for products resulting in leave-on dermal exposure is 0.35% PPG-2 Hydroxyethyl Cocamide in face and neck products.[24]

Use concentration data were reported for PEG-3 Lauramide, PEG-6 Lauramide, and PEG-50 Tallow Amide in response to the Council surveys, but no uses were received in the VCRP; it should be presumed there is at least one use in every category for which a use concentration is reported. Additionally, uses were reported in the VCRP for PEG-3 Cocamide and PEG-5 Cocamide, but no concentrations of use were reported for these ingredients in the industry survey. The ingredients not in use, according to both the 2019 VCRP data and the industry survey, are listed in Table 5.

The majority of the in-use alkoxylated fatty amides have uses that result in contact with the mucous membranes; for example, PEG-6 Lauramide and PPG-2 Cocamide are used in bath soaps and detergents at up to 4%.[24] According to the Council survey, PPG-2 Cocamide is used in aerosol hair spray formulations at a maximum concentration of 0.8%, and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[26,27] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[28,29]

The alkoxylated fatty amides are not restricted from use in any way under the rules governing cosmetic products in the European Union.[30]

Exposure Assessment

PEG-4 Rapeseedamide

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

NICNAS also calculated an equivalent daily systemic exposure of PEG-4 Rapeseedamide from use in hair dyes. Considering typical exposure to hair dye as 20 mg/cm^2 product applied to a scalp surface area of 580 cm^2, for a hair dye containing 15% PEG-4 Rapeseedamide, it was estimated that 1740 mg PEG-4 Rapeseedamide was used per application. Using a retention factor of 0.1, body weight of 60 kg, dermal absorption of 100%, and frequency of use of one application per 28 days, the equivalent daily systemic exposure was determined to be 0.10 mg/kg bw/day for a hair dye containing 15% PEG-4 Rapeseedamide.

Combining these two exposures, the total potential systemic exposure to PEG-4 Rapeseedamide was calculated as 1.48 mg/kg bw/day. (It should be noted that the concentrations used by NICNAS to calculate daily exposure are greater than those reported in the Council use survey.) For the MOE calculation, a no-observable-adverse-effect-level (NOAEL) of 150 mg/kg bw/day (derived in a 28-day oral toxicity study in rats, described later in this report, and using the value for female rats because the effects at 15 mg/kg bw/day in male rats were minimal) was used.

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

An MOE value ≥ 100 is considered acceptable to account for intra- and inter-species differences. Therefore the MOE for PEG-4 Rapeseedamide was considered acceptable.

PPG-2 Hydroxyethyl Cocamide

NICNAS estimated exposure to PPG-2 Hydroxyethyl Cocamide through shampoo use.[7] Assuming application of 12 g of shampoo containing 4% PPG-2 Hydroxyethyl Cocamide, a body weight of 60 kg, and 10% dermal absorption, exposure is calculated as 0.8 mg/kg/d PPG-2 Hydroxyethyl Cocamide. In comparison to a no-observable-effect-level (NOEL) of 15 mg/kg/d determined in a 28-day oral study in rats (described later in this report), the calculated human exposure is below the NOEL value.

The CIR Science and Support Committee (SSC) calculated MOEs for a leave-on face product containing 0.35% PPG-2 Hydroxyethyl Cocamide and for a leave-on hair styling product containing 7.5% PPG-2 Hydroxyethyl Cocamide.[31] Assuming the 95th percentile use of a face lotion (3.99 g/day), the estimated exposure from a face product containing 0.35% PPG-2 Hydroxyethyl Cocamide is 0.24 mg/kg bw/d. Considered default assumptions for leave on hair products (5.74 mg/kg bw/d), the estimated exposure from a leave-on hair styling product containing 7.5% PPG-2 Hydroxyethyl Cocamide is 0.43 mg/kg bw/d. For the MOE calculations, the CIR SSC used the most conservative NOAEL value from a 28-day oral toxicity study that was available for this group of ingredients, which was 150 mg/kg bw/day from the study on PEG-4 Rapeseedamide. (In the 28-day oral rat study of PPG-2 Hydroxyethyl Cocamide, the NOAEL was 1000 mg/kg/day.)

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

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

Non-Cosmetic

PEG-4 Rapeseedamide is used in industrial dishwashing and laundry care.[32] Other industrial uses include as an additive in metal working fluids, as an emulsifier and metal corrosion protector, and in photochemicals as an emulsifier.[8]

TOXICOKINETICS

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute toxicity studies summarized below[7-9,33] are described in Table 6.

The dermal LD_{50}s of PEG-4 Rapeseedamide (60 - 80% pure) and PPG-2 Hydroxyethyl Cocamide in Sprague-Dawley rats were > 2000 mg/kg. In rats, the oral LD_{50}s of PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (a component of PPG-2 Hydroxyethyl Coco/Isostearamide) were > 2000 mg/kg. In both the dermal and the oral studies, this was the highest dose tested. In inhalation studies of PEG-4 Rapeseedamide (60 - 80% pure), groups of two Wistar rats were exposed to 4.92 mg/l (actual concentration) of the test article for 0.5 - 4 h, and groups of six Wistar rats were exposed to 6 mg/l (actual concentration) of the test article for 4 h, via oronasal exposure. Some deaths were reported in the first study, but not the second study, and the LC_{50}s were reported to be 1 - 5 mg/L/4 h and > 6 mg/L/4 h, respectively.

Short-Term Toxicity Studies

Oral

PEG-4 Rapeseedamide

Groups of 5 male and 5 female Sprague-Dawley rats were dosed by gavage with 0, 15, 150, or 1000 mg/kg bw/day (PEG-4 Rapeseedamide 60 - 80% pure) in arachis oil for 28 days, in accord with Organisation for Economic Co-operation and Development test guideline (OECD TG) 407.[8] All animals survived until study termination. A statistically significant reduction in body weights was observed in females of the mid-dose group during wk 2; a non-statistically significant reduction in body weight gain and food consumption, when compared with controls, was reported for males of the high-dose group. No treatment related behavioral, functional performance, or sensory reactivity changes were observed. No toxicologically-significant changes in clinical chemistry, hematology, or urinalysis parameters were reported. A statistically significant, non-dose dependent, reduction in absolute thymus weights was observed in low- and high-dose males. Microscopic forestomach lesions (acanthosis and hyperkeratosis, occasionally with associated subepithelial inflammatory cell infiltrates) in high dose males were attributed to slight irritancy of the test material, and cortical hypertrophy of the adrenal glands observed in 3 females in the high dose group may reflect a non-specific stress response to the irritancy of the test material. The NOAELs were 15 and 150 mg/kg bw/day for male and female rats, respectively.

PPG-2 Hydroxyethyl Cocamide

Groups of 3 male and 3 female albino rats were dosed with 0, 100, 500, or 1000 mg/kg/day PPG-2 Hydroxyethyl Cocamide by gavage for 7 days, in accord with OECD TG 407.[7] The vehicle was not specified. All animals survived until study termination. Transient salivation noted with the highest doses was considered unremarkable. There were no effects on kidney, liver, or spleen weights. No gross lesions were observed at necropsy. Clinical chemistry, hematology, and microscopic studies were not conducted. No evidence of toxicity was observed.

In a 28-day study conducted in accord with OECD TG 407, groups of 5 male and 5 female albino rats were dosed by gavage with 0, 15, 150, or 1000 mg/kg/day PPG-2 Hydroxyethyl Cocamide for 28 days.[7] The vehicle was not specified. No mortalities were reported. Transient post-dosing salivation was observed in some animals of all test groups. No treatment-related changes were reported for clinical chemistry or hematology parameters. Changes in urinary parameters included a decrease in urine volume and in urinary phosphorus and an increase in urinary pH in high-dose males, and a decrease in urinary potassium in high-dose males and high- and mid-dose females; these changes were not supported by pathological changes. Slight decreases in absolute and relative thymus weights were not considered to be toxicologically significant. Focal basophilic cortical tubules observed in three high dose male rats were not considered treatment-related. The NOEL was 15 mg/kg/day, and the NOAEL was 1000 mg/kg/day.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

PEG-4 Rapeseedamide

A reproductive/developmental toxicity screening test was performed in accord with OECD TG 421 using groups of 10 male and 10 female rats that were dosed with 0, 15, 150, or 500 mg/kg bw/day PEG-4 Rapeseedamide (60 - 80% pure) in arachis oil by gavage for 55 days.[8] Animals were paired for mating on day 15 of dosing. Males were killed on day 43; females were allowed to litter, and were killed on 5 days post-partum. No mortalities were reported. No adverse effects on parental body weights, mating performance, fertility, or length of gestation were reported, and there were no effects on litter size, total litter weights, sex ratio, or viability of offspring. The NOAEL was 500 mg/kg bw/day.

GENOTOXICITY STUDIES

The genotoxicity studies summarized below[7-9] are also described in Table 7.

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

In the mouse micronucleus test, PEG-4 Rapeseedamide (60 - 80% pure) dosed orally at ≤ 400 mg/kg bw in arachis oil[8] and aq. PPG-2 Hydroxyethyl Cocamide dosed intraperitoneally at ≤ 1000 mg/kg were not clastogenic.[7] Additionally, in Sprague-Dawley rats, dosing with up to 2000 mg/kg aq. PPG-2 Hydroxyethyl Cocamide by gavage did not induce DNA damage.

CARCINOGENICITY STUDIES

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

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below[7,8,34,35] are also described in Table 8.

Undiluted PEG-4 Rapeseedamide (60 - 80% pure) was irritating, but not corrosive, to rabbit skin; duration of dosing was not specified. Undiluted PPG-2 Hydroxyethyl Cocamide applied to rabbit skin for 4 h (2.5 cm^2 patches containing 0.5 ml test material) was classified as irritating, produced thickening of the skin, desquamation, and well-defined erythema, but 3-min and 1-h exposures were not irritating. In Magnusson-Kligman maximization studies in guinea pigs, PEG-4 Rapeseedamide (60 - 80% pure; intradermal induction 0.2%, topical induction – 10%, topical challenge – 0.01%; in sesame oil) and PPG-2 Hydroxyethyl Cocamide (intradermal induction – 0.5%, topical induction – 50%, topical challenge – 5 and 10%; in water) were not sensitizers.

In clinical testing, 0.5% aq. PEG-4 Rapeseedamide (60 - 80% pure; 2 cm^2 patches containing 0.2 ml test material) was not a sensitizer in a human repeated insult patch test (HRIPT), and 5% aq. PPG-2 Hydroxyethyl Cocamide (4.5 cm^2 patches containing 0.2 ml test material) was not an irritant. Both studies were performed using 50 subjects.

OCULAR IRRITATION STUDIES

Animal

PEG-4 Rapeseedamide

The ocular irritation potential of PEG-4 Rapeseedamide (60 - 80% pure) was evaluated in three New Zealand White rabbits in an acute eye irritation/corrosion test (OECD TG 405).[8] The undiluted test material was instilled into the conjunctival sac of one eye of each animal, and the eyes were observed for 7 days. The test material was slightly irritating to rabbit eyes. The mean scores (calculated using the 24, 48, and 72 h scores for each animal) for the conjunctiva ranged from 1.3 - 1.7/2 for redness; 0 - 0.7/1 for chemosis; and 0.3 (all animals)/1 for discharge; irritation resolved within 7 days. Corneal opacity and iridial inflammation were not observed.

PPG-2 Hydroxyethyl Cocamide

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

CLINICAL STUDIES

Case Reports

PEG-4 Rapeseedamide

A female patient developed dermatitis 1 month after exposure to massage oils while working as a masseuse, and presented with eczema on the flexor wrist and forearm of 4 mos duration.[36] Patch testing was conducted using a standard series and with oils from work. Two massage oils from the same manufacturer produced positive reactions. Subsequent testing with components of those oils resulted in positive reactions to 3.0% PEG-4 Rapeseedamide. Positive reactions were also reported in a dilution series with PEG-4 Rapeseedamide; "+++" reactions were observed with 0.003 - 3.0% in petrolatum and 0.03 -

3% aq., and a "+" reaction was observed with 0.003% aq. PEG-4 Rapeseedamide. Control subjects (n = 28) did not react to 0.3% PEG-4 Rapeseedamide in petrolatum.

SUMMARY

This assessment reviews the safety of 40 alkoxylated fatty amides as used in cosmetics. These ingredients are alkoxylated simple amides, and most of these alkoxylated fatty amides are mono-*N*-alkoxyl-substituted. However, a few of the ingredients (such as PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA) are di-*N*,*N*-alkoxyl-substituted amides. The ingredients reviewed in this report are classic non-ionic surfactants, with a hydrophobic fatty alkyl tail on one end and a hydrophilic, non-ionic, alkoxylated head group on the other end.

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

Using GC/MS analysis, PEG-50 Hydrogenated Palmamide contains less than 50 ppm of residual monoethylene glycol or diethylene glycol. One supplier reports that PEG-4 Rapeseedamide is 92 - 93% active matter, and specifications for the presence of 1,4-dioxane are 1 ppm. According to NICNAS, the degree of purity of PEG-4 Rapeseedamide (as the raw material) is 60 – 80% pure and low levels of 1,4 dioxane (down to 100 mg/kg or 100 mg/l) may be present. PPG-2 Hydroxyethyl Cocamide is reported to be > 90% pure; methanol levels are typically < 300 ppm, and heavy metals testing reported levels of < 0.5 ppm

Twelve of the 40 ingredients included in this assessment are reported to be in use. PPG-2 Hydroxyethyl Cocamide has the greatest reported frequency of use (354 formulations), and PEG-4 Rapeseedamide has the second greatest reported number of uses (301). The alkoxylated fatty amides are primarily used in rinse-off formulations, and most of the reported uses are in some type of hair or cleansing formulation. PEG-4 Rapeseedamide has the highest concentration of use, at 9.3% in hair dyes and colors. PPG-2 Hydroxyethyl Cocamide has the next highest reported concentration of use is; it is used at 7.5% in "other" non-coloring hair preparations. There are some uses that result in leave-on dermal exposure; the highest concentration of use reported for products resulting in leave-on dermal exposure is 0.35% PPG-2 Hydroxyethyl Cocamide in face and neck products. The majority of the in-use alkoxylated fatty amides have uses that result in contact with the mucous membranes; for example, PEG-6 Lauramide and PPG-2 Cocamide are used in bath soaps and detergents at up to 4%. According to the Council survey, PPG-2 Cocamide is used in aerosol hair spray formulations at a maximum concentration of 0.8%, and could possibly be inhaled.

MOEs were calculated for PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide. The MOE for PEG-4 Rapeseedamide, considering combined use in six rinse-off products and in a hair dye (with use concentrations that are greater than those reported in the Council use survey), was 101. For PPG-2 Hydroxyethyl Cocamide, an MOE of 625 was calculated for a face product containing 0.35%, and a MOE of 349 was calculated for a leave-on hair styling product containing 7.5% PPG-2 Hydroxyethyl Cocamide.

The dermal LD_{50}s of PEG-4 Rapeseedamide (60 - 80% pure) and PPG-2 Hydroxyethyl Cocamide in Sprague-Dawley rats were > 2000 mg/kg. In rats, the oral LD_{50}s of PEG-4 Rapeseedamide (60 - 80% pure), PPG-2 Hydroxyethyl Cocamide, and PPG-2 hydroxyethyl isostearamide (a component of PPG-2 Hydroxyethyl Coco/Isostearamide) were > 2000 mg/kg. In both the dermal and the oral studies, this was the highest dose tested. In inhalation studies of PEG-4 Rapeseedamide (60 - 80% pure), groups of two Wistar rats were exposed to 4.92 mg/l (actual concentration) of the test article for 0.5 - 4 h, and groups of six Wistar rats were exposed to 6 mg/l (actual concentration) of the test article for 4 h, via oronasal exposure. Some deaths were reported in the first, but not the second, study and the LC_{50}s were reported to be 1 - 5 mg/L/4 h and > 6 mg/L/4 h, respectively.

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

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

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

Undiluted PEG-4 Rapeseedamide (60 - 80% pure) was irritating, but not corrosive, to rabbit skin; duration of dosing was not specified. Undiluted PPG-2 Hydroxyethyl Cocamide applied to rabbit skin for 4 h (2.5 cm^2 patches containing 0.5 ml test material) was classified as irritating, produced thickening of the skin, desquamation, and well-defined erythema, but 3-min and 1-h exposures were not irritating. In Magnusson-Kligman maximization studies in guinea pigs, PEG-4 Rapeseedamide (60 - 80% pure; intradermal induction 0.2%, topical induction – 10%, topical challenge – 0.01%; in sesame oil) and PPG-2 Hydroxyethyl Cocamide (intradermal induction – 0.5%, topical induction – 50%, topical challenge – 5 and 10%; in water) were not sensitizers.

In clinical testing, 0.5% aq. PEG-4 Rapeseedamide (60 - 80% pure; 2 cm^2 patches containing 0.2 ml test material) was not a sensitizer in an HRIPT, and 5% aq. PPG-2 Hydroxyethyl Cocamide (4.5 cm^2 patches containing 0.2 ml test material) was not an irritant. Both studies were performed using 50 subjects.

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

DISCUSSION

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

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

The Panel was concerned that the potential exists for dermal irritation with the use of products formulated using alkoxylated fatty amides. The Panel specified that products containing alkoxylated fatty amides must be formulated to be non-irritating.

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

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

The Panel also discussed the issues of impurities that could be of concern with this group of ingredients. The possible presence of 1,4-dioxane as an impurity is one concern. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit this impurity in alkoxylated fatty amide ingredients before blending them into cosmetic formulations. Additionally, manufacturers should minimize primary amine impurities, and the Panel specified that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed. The Panel acknowledged that some of the alkoxylated fatty amides may be formed from plant-derived or animal-derived constituents. The Panel thus

expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to sufficiently limit amounts of such impurities in these ingredient before blending them into cosmetic formulations. Additionally, the Panel considered the risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. While tallow may be used in the manufacture of some ingredients in this safety assessment and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the US FDA that tallow derivatives are not risk materials for transmission of infectious agents.

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

CONCLUSION

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

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

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

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

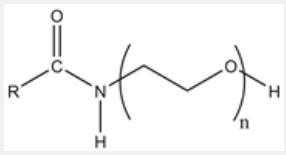
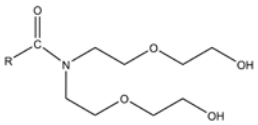
Ingredient CAS No.	Definition & Structure*	Function(s)
Ethoxylated	***General formula:*** 	
PEG-2 Cocamide [61791-08-0 (generic to PEG-x Cocamides)]	PEG-2 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 2.	surfactant - emulsifying agent; surfactant - foam booster
PEG-3 Cocamide 61791-08-0 (generic)	PEG-3 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster
PEG-4 Cocamide [61791-08-0 (generic to PEG-x Cocamides)]	PEG-4 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 4.	surfactant - emulsifying agent
PEG-5 Cocamide 61791-08-0 (generic)	PEG-5 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 5.	surfactant - emulsifying agent
PEG-6 Cocamide 61791-08-0 (generic)	PEG-6 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 6.	surfactant - emulsifying agent
PEG-7 Cocamide 61791-08-0 (generic)	PEG-7 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 7.	surfactant - emulsifying agent
PEG-11 Cocamide 61791-08-0 (generic)	PEG-11 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 11.	surfactant - cleansing agent; surfactant - emulsifying agent
PEG-20 Cocamide 61791-08-0 (generic)	PEG-20 Cocamide is the polyethylene glycol amide of coconut acid that conforms generally to the above formula, and RCO- represents the fatty acids derived from coconut oil and n has an average value of 20.	surfactant - emulsifying agent
PEG-3 Cocamide DEA	PEG-3 Cocamide DEA is the polyethylene glycol derivative of Cocamide DEA with an average of 3 moles of ethylene oxide. [Cocamide DEA is a mixture of ethanolamides of coconut acid. It conforms generally to the formula:  where RCO- represents the fatty acids derived from *Cocos nucifera* (coconut) oil.]	surfactant - emulsifying agent
PEG-20 Cocamide MEA	PEG-20 Cocamide MEA is the polyethylene glycol derivative of cocamide MEA containing an average of 20 moles of ethylene oxide. [Cocamide MEA is a mixture of ethanolamides of coconut acid. It conforms generally to the above general formula, and RCO- represents the fatty acids derived from *Cocos nucifera* (coconut) oil.]	surfactant - emulsifying agent
PEG-6 Hydrogenated Palmamide	PEG-6 Hydrogenated Palmamide is the polyethylene glycol amide of hydrogenated palm oil that generally to the above formula, and RCO- represents the fatty acids derived from hydrogenated palm oil and n has an average value of 6.	emulsion stabilizer; surfactant - emulsifying agent
PEG-50 Hydrogenated Palmamide	PEG-50 Hydrogenated Palmamide is the polyethylene glycol amide of hydrogenated palm oil that conforms generally to the above formula, and RCO- represents the fatty acids from hydrogenated palm oil and n has an average value of 50.	cleansing agent; surfactant - solubilizing agent
PEG-13 Hydrogenated Tallow Amide 68783-22-2 (generic)	PEG-13 Hydrogenated Tallow Amide is the polyethylene glycol amide of hydrogenated tallow amide that conforms generally to the above formula, and RCO- represents the fatty acids derived from hydrogenated tallow and n has an average value of 13.	surfactant - emulsifying agent
PEG-5 Lanolinamide	PEG-5 Lanolinamide is the polyethylene glycol amide of lanolin acid with an average of 5 [stoichiometric equivalents] of ethylene oxide. [PEG-5 Lanolinamide conforms generally to the above formula, and RCO- represents the fatty acids derived from Lanolin Acid (a mixture of organic acids obtained from the hydrolysis of Lanolin) and n has an average value of 5]	hair conditioning agent; viscosity increasing agent - nonaqueous

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

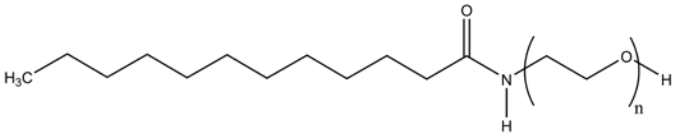
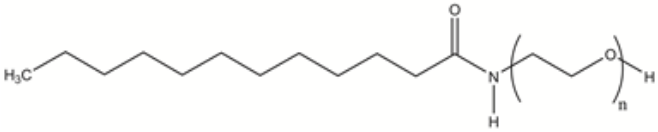
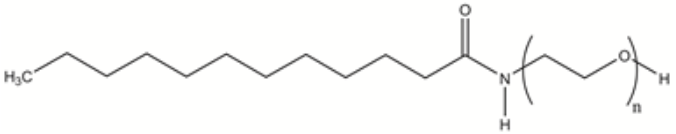
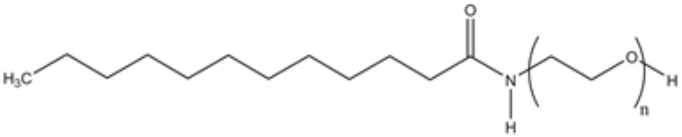
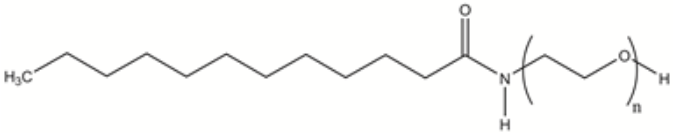
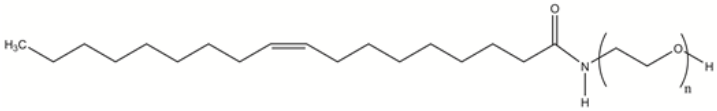
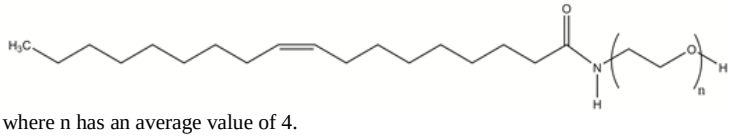
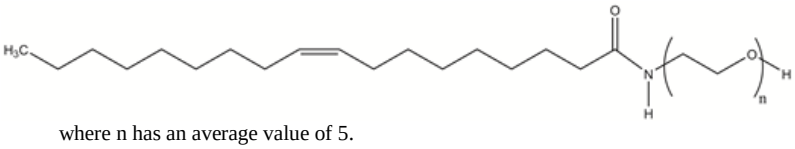
Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-2 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-2 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:  where n has an average value of 2.	surfactant - cleansing agent; surfactant - emulsifying agent
PEG-3 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-3 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:  where n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster
PEG-5 Lauramide 26635-75-6 (generic)	PEG-5 Lauramide is the polyethylene glycol amide of lauric acid that conforms generally to the formula:  where n has an average value of 5.	surfactant - emulsifying agent
PEG-6 Lauramide 26635-75-6 (generic)	PEG-6 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:  where n has an average value of 6.	surfactant - emulsifying agent
PEG-11 Lauramide [26635-75-6 (generic to PEG-x Lauramides)]	PEG-11 Lauramide is the polyethylene glycol amide of lauric acid that conforms to the formula:  where n has an average value of 11.	surfactant - emulsifying agent
PEG-3 Oleamide	PEG-3 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 3.	surfactant - emulsifying agent; surfactant - foam booster
PEG-4 Oleamide	PEG-4 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 4.	surfactant - emulsifying agent
PEG-5 Oleamide	PEG-5 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 5.	surfactant - emulsifying agent

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

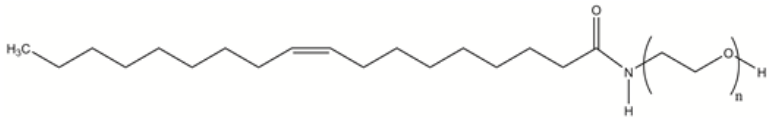
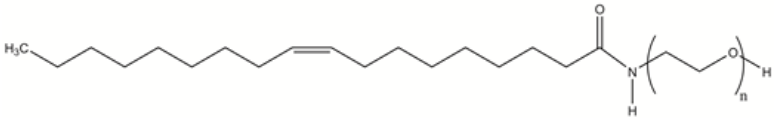
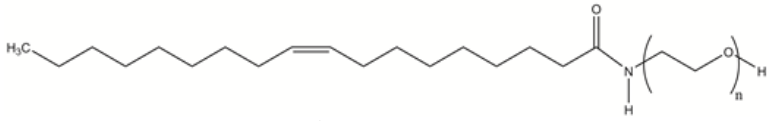
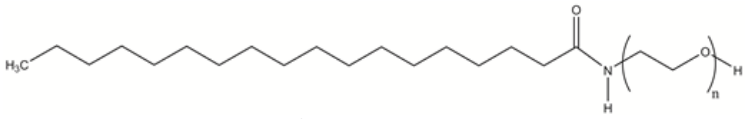
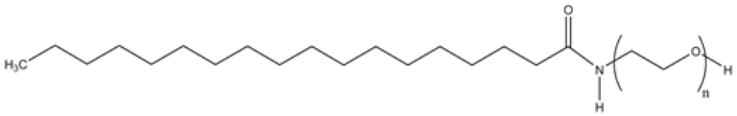
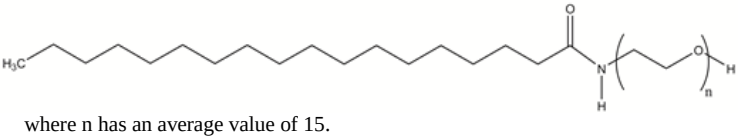
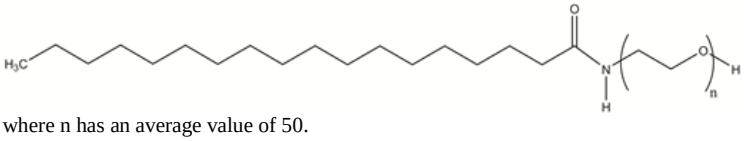
Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-6 Oleamide	PEG-6 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 6	surfactant - emulsifying agent
PEG-7 Oleamide	PEG-7 Oleamide is the polyethylene glycol amide of oleic acid that conforms to the formula:  where n has an average value of 7.	surfactant - emulsifying agent
PEG-9 Oleamide	PEG-9 Oleamide is the polyethylene glycol amide of oleic acid that conforms generally to the formula:  where n has an average value of 9.	surfactant - emulsifying agent
PEG-4 Rapeseedamide 85536-23-8	PEG-4 Rapeseedamide is the polyethylene glycol amide of the fatty acids derived from rapeseed oil with an average of 4 moles of ethylene oxide. [Rapeseed Acid is a mixture of fatty acids derived from *Brassica campestris* (rapeseed) seed oil. PEG-4 Rapeseedamide conforms generally to the above general formula, and RCO- represents the fatty acids from rapeseed oil and n has an average value of 4.]	surfactant - emulsifying agent; viscosity increasing agent - aqueous
PEG-4 Stearamide	PEG-4 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:  where n has an average value of 4.	surfactant - emulsifying agent
PEG-10 Stearamide	PEG-10 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:  where n has an average value of 10.	surfactant - emulsifying agent
PEG-15 Stearamide	PEG-15 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:  where n has an average value of 15.	surfactant - emulsifying agent
PEG-50 Stearamide	PEG-50 Stearamide is the polyethylene glycol amide of stearic acid that conforms generally to the formula:  where n has an average value of 50.	skin-conditioning agent - miscellaneous
PEG-5 Tallow Amide 8051-61-4	PEG-5 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 5.	antistatic agent; surfactant - emulsifying agent
PEG-8 Tallow Amide	PEG-8 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 8.	surfactant - emulsifying agent

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

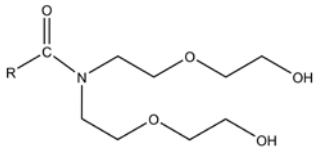
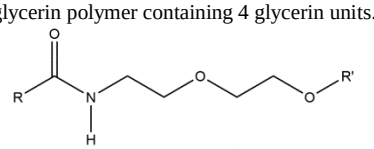
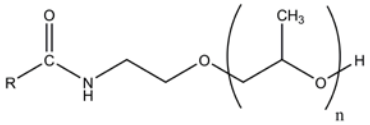
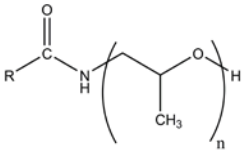
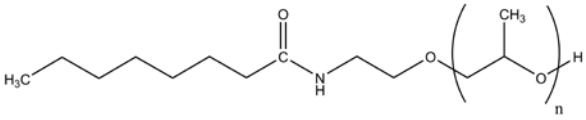
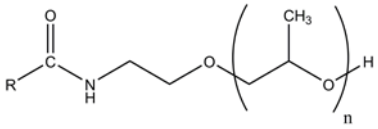
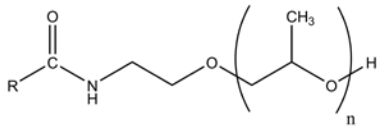
Ingredient CAS No.	Definition & Structure*	Function(s)
PEG-50 Tallow Amide 8051-63-6	PEG-50 Tallow Amide is the polyethylene glycol amide of tallow acid that conforms generally to the above general formula, and RCO- represents the fatty acids derived from tallow and n has an average value of 50.	surfactant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

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

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

*see Table 2 for available fatty acid composition

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

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

Table 3. Physical and Chemical Properties

Property	Value	Reference
PEG-6 Cocamide		
Physical Form (@ 25°C)	liquid	15
Color (@ 30°C)	clear	16
Density (g/ml @ 25 ºC)	0.99	15,16
Viscosity (kg/(s x m) @ 25ºC; @ 60°C)	0.217; 0.039	16
Vapor pressure (mmHg @ 20 ºC)	0.01	15
Boiling Point (ºC)	100	15
Hydrophilic-Lipophilic Balance (HLB)	14.6	15,16
PEG-4 Rapeseedamide		
Physical Form	clear liquid	17
Color	yellow	17
Molecular Weight (g/mol)	< 600	8
Density/Specific Gravity (kg/m^3; @ 20ºC)	997	8
Refraction Index (n_D^{25})	1.4675 – 1.4705	21
Viscosity (mPa.s @ 20°C)	< 500	21
Vapor pressure (mm Hg)	0.0019	8
Melting Point (ºC)	5-10	8
Boiling Point (ºC)	> 262	8
Water Solubility (g/L @ 23 ºC)	9.0 x 10^{-4}	8
Other Solubility (g/L @ 20ºC)	652 – 702 in *n*-octanol	8
log K_{ow}	> 2.57 (the compound is surface active and is expected to partition to phase boundaries)	8
HLB	~11	17
PPG-2 Hydroxyethyl Cocamide		
Physical Form	liquid	7
Color	yellowish	7
Specific Gravity (@ 20 ºC)	0.98	7
Vapor pressure (mmHg 25 ºC)	5.25 x 10^{-5}	7
Boiling Point (ºC)	> 165 (decomposition occurs over the range 60 - 305)	7
Water Solubility (g/L @ 20 ºC)	< 0.001	7
log K_{ow}	0.86 to > 6.2 * (the high variability is due to the surfactant nature of this ingredient)	7

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

Table 4. Frequency[23] and concentration[24,25] of use according to duration and type of exposure

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	PEG-2 Cocamide		**PEG-3 Cocamide**		**PEG-5 Cocamide**	
Totals*	**2**	**0.12-2**	**3**	**NR**	**20**	**NR**
Duration of Use						
Leave-On	*NR*	*NR*	*2*	*NR*	*NR*	*NR*
Rinse-Off	*2*	*0.12-2*	*1*	*NR*	*20*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	2[a]	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	2	0.3-2	3	NR	18	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.12	NR	NR	2	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.3-2	NR	NR	18	NR
Baby Products	NR	NR	NR	NR	NR	NR
	PEG-6 Cocamide		**PEG-50 Hydrogenated Palmamide**		**PEG-3 Lauramide**	
Totals*	**20**	**0.75-2**	**26**	**1-3**	**NR**	**4**
Duration of Use						
Leave-On	*NR*	*NR*	*NR*	*1*	*NR*	*NR*
Rinse Off	*20*	*0.75-2*	*26*	*2-3*	*NR*	*4*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	18	2	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	0.75-0.8	NR	1	NR	4
Hair-Coloring	NR	NR	26	2-3	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	18	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	PEG-6 Lauramide		**PEG-4 Rapeseedamide**		**PEG-50 Tallow Amide**	
Totals*	**NR**	**4**	**301**	**0.93-9.3**	**NR**	**2**
Duration of Use						
Leave-On	*NR*	*NR*	*5*	*NR*	*NR*	*NR*
Rinse-Off	*NR*	*4*	*293*	*0.93-9.3*	*NR*	*2*
Diluted for (Bath) Use	*NR*	*NR*	*3*	*2*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1[a]	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	4	66	0.93-3	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	54	2.4-2.8	NR	NR
Hair-Coloring	NR	NR	178	8.2-9.3	NR	2
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	4	66	1-3	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 4. Frequency[23] and concentration[24,25] of use according to duration and type of exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	PPG-2 Cocamide		**PPG-2 Hydroxyethyl Cocamide**		**PPG-2 Hydroxyethyl Coco/Isostearamide**	
Totals	**3**	**0.8-4**	**354**	**0.00025-7.5**	**26**	**0.5-3**
Duration of Use						
Leave-On	*NR*	*0.8*	*6*	*0.35-7.5*	*NR*	*NR*
Rinse Off	*3*	*2-4*	*338*	*0.00025-4*	*26*	*0.5-3*
Diluted for (Bath) Use	*NR*	*NR*	*10*	*1.5-3*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	0.8	1[a]	0.62[a]	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	0.35[b]	NR	NR
Dermal Contact	1	4	320	0.008-4	14	0.5-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	0.8-2	34	0.00025-7.5	11	NR
Hair-Coloring	NR	NR	NR	NR	1	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	4	291	1.5-3	6	0.5-0.6
Baby Products	NR	NR	3	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – no reported use

Table 5. Ingredients not reported to be in use (according to VCRP and Council survey data)[23-25]

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

Table 6. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose	Protocol	LD_{50} or LC_{50}/Results	Reference
				DERMAL			
PEG-4 Rapeseedamide (60 - 80% pure)	Sprague-Dawley rats	5/sex	none specified	2000 mg/kg	semi-occlusive application (OECD TG 402)	> 2000 mg/kg no dermal irritation and no signs of toxicity were observed	8
PPG-2 Hydroxyethyl Cocamide	Sprague-Dawley rats	5/sex	none	2000 mg/kg	24-h patch; porous gauze covered with a waterproof dressing (OECD TG 402)	> 2000 mg/kg slight to well-defined erythema (7 animals) and edema (6 animals) was resolved by day 9 and 8, respectively; desquamation with scabbing was observed in 2 females	33
				ORAL			
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	5/sex	none specified	2000 mg/kg	by gavage (OECD TG 401)	> 2000 mg/kg no signs of toxicity were observed	8
PPG-2 Hydroxyethyl Cocamide	Sprague-Dawley rats	3/sex	none specified	2000 mg/kg	by gavage (OECD TG 401)	> 2000 mg/kg	7
PPG-2 hydroxyethyl isostearamide (a component of PPG-2 Hydroxyethyl Coco/Isostearamide)	Sprague-Dawley rats	3/sex	1% (w/v) aq. methylcellulose	2000 mg/kg	by gavage (OECD TG 423)	> 2000 mg/kg	9
				INHALATION			
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	2 males	none specified	24.34 mg/l (nominal); 4.92 mg/l (actual)	oronasal exposure (OECD TG 403) 0.5, 1, 2, or 4 h exposure period 2.14 µm particle size	1-5 mg/L/4 h labored and noisy breathing was observed 1 animal exposed for 2 h and 1 exposed for 4 h died 1 day after exposure; discolored non-collapsed lungs, mottled liver, dilatation of the kidneys and intestine were observed at necropsy	8
PEG-4 Rapeseedamide (60 - 80% pure)	Wistar rats	3/sex	none specified	119 mg/l (nominal); 6 mg/l (actual)	oronasal exposure (OECD TG 436) 4 h exposure period; 2.05-2.14 µm particle size	> 6 mg/L/4 h labored breathing was observed in all males and in one female (day 2); no mortality	8

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

Table 7. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
PEG-4 Rapeseedamide (60 - 80% pure)	312.5 - 5000 µg/plate, with and without metabolic activation	DMSO	*Salmonella typhimurium* TA1538, TA1535, TA1537, TA98, TA100	Ames test (OECD TG 471)	not mutagenic	8
PEG-4 Rapeseedamide (60 - 80% pure)	39 - 5000 µg/ml, with and without metabolic activation	DMSO	human cultured peripheral lymphocytes	mammalian chromosomal aberration test (OECD TG 473)	not clastogenic	8
PPG-2 Hydroxyethyl Cocamide	1.5 - 5000 µg/plate, with and without metabolic activation	not stated	*S. typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* CM891	Ames test (OECD TG 471)	not mutagenic	7
PPG-2 Hydroxyethyl Cocamide	with activation: 125 - 300 µg/ml initial study; 3 h); 300 -500 µg/ml (confirmation; 3 h); 450 and 500 µg/ml (confirmation 2; 3 h) without metabolic activation: 62.5 - 250 µg/ml (initial study; 3 h); 62.5 - 125 µg/ml (confirmation; 21 h)	water	human lymphocytes	mammalian chromosomal aberration test (OECD TG 473)	"not likely to be clastogenic" with metabolic activation, statistically significant increase in proportion of metaphase figures with chromosomal aberrations at 450 and 500 µg/ml in both confirmation studies; these were cytotoxic concentrations all other results were negative	7
PPG-2 hydroxyethyl isostearamide (a component of PPG-2 Hydroxyethyl Coco/Isostearamide)	5 - 5000 µg/plate, with and without metabolic activation	DMSO	*S. typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2*uvr*A	Ames test (OECD TG 471)	not mutagenic	9
IN VIVO						
PEG-4 Rapeseedamide (60-80% pure)	0, 100, 200, and 400 mg/kg bw (24 h) 0 and 400 mg/kg bw (48 h)	arachis oil	albino Crl:CD-1 mice; 7/sex test animals; 14/sex negative controls; 5/sex positive controls	micronucleus test (OECD TG 474) animals were dosed by gavage cyclophosphamide served as the positive control	not clastogenic no statistically significant decreases in PCE/NCE ratios; however, marked decreases is the PCE/NCE ratio was observed in the 200 (24h) and 400 (48 h) mg/kg bw groups clinical signs were reported in the 200 and 400 mg/kg bw dose groups	8
PPG-2 Hydroxyethyl Cocamide	0, 250, 500, and 1000 mg/kg	water	CD-1 outbred albino mice; 10 males in the control and high dose groups; 5 males in the low and mid dose groups	micronucleus test (OECD TG 474) animals were dosed intraperitoneally positive control not identified	not clastogenic	7
PPG-2 Hydroxyethyl Cocamide	0, 600, and 2000 mg/kg	water	Sprague-Dawley rats; 5 males per group	rat liver DNA repair (UDS) test (OECD TG 486) animals were dosed by gavage	did not induce DNA damage	7

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

Table 8. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
PEG-4 Rapeseedamide (60 - 80% pure)	applied neat	3 female NZW rabbits	semi-occlusive application; animals were observed for 22 days (OECD TG 404) duration of dosing was not stated; however, according to the TG, dosing is typically 4 h in duration	irritating; no corrosive effect; no systemic toxicity mean scores (calculated using the 24, 48, and 72 h scores for each animal) ranged from 2-4/4 for erythema and 2-2.7/3 for edema irritation did not resolve by study termination	8
PEG-4 Rapeseedamide (60 - 80% pure)	intradermal induction – 0.2% topical induction – 10% topical challenge – 0.01% vehicle – sesame oil	10 (test) or 5 (control) male Dunkin Hartley guinea pigs	skin sensitization – maximization test (OECD TG 406)	not sensitizing	8
PPG-2 Hydroxyethyl Cocamide	applied neat	3 male NZW rabbits	4 h semi-occlusive patch; 0.5 ml applied to a 2.5 cm^2 area using a porous gauze pad covered with elastic adhesive dressing (OECD TG 404) 1 animal also received 3 min and 1 h applications	4 h exposure: irritating to rabbit skin thickening of the skin, desquamation, and well-defined erythema in all 3 animals; did not resolve in 2/3 animals by day 14, with very slight erythema observed 3 min and 1 h exposure: no irritation	34
PPG-2 Hydroxyethyl Cocamide	intradermal induction – 0.5% topical induction – 50% topical challenge – 5 and 10% vehicle – water	10 (test) or 5 (control) female Dunkin Hartley guinea pigs	Magnusson-Kligman maximization test (OECD TG 406) intradermal induction (day 0) consisted of 3 pairs of 0.1 ml injections: FCA/water 1:1; test substance only; test substance in FCA/saline 1:1 topical induction (day 7), 48 h occlusive patch (0.4 ml) challenge (day 21), 24 h occlusive patches (0.2 ml)	not sensitizing no irritation following topical applications; slight irritation at injection site after injection of test substance or sterile water (control animals)	35
			HUMAN		
PEG-4 Rapeseedamide (60 - 80% pure)	0.5% aq.	50 subjects	HRIPT induction: 2 cm^2 patches containing 0.2 ml test material were applied for 24 h (3x/wk for 3 wks), and the test sites were assessed 24 or 48 h after removal challenge: after a 2 wk non-treatment period, 1 test patch was applied for 24 h to a previously untreated site; the site was assessed 24, 48, and 72 h after application	not an irritant or sensitizer one instance of barely perceptible or spotty erythema for 3 subjects	8
PPG-2 Hydroxyethyl Cocamide	5% aq.	50 subjects	48 h occlusive patch; 0.2 ml applied via a 4.5 cm^2 gauze pad; test sites were evaluated at patch removal and after 24 h procedure was repeated using occlusive and semi-occlusive patches in subjects with positive responses	not irritating one subject had a mild and one a moderate response 24 h after patch removal; both subjects had mild responses 48 h after patch removal with follow-up testing, one subject had a positive response with the occlusive patch, but a negative response with the semi-occlusive patch	7

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

REFERENCES

1. Nikitakis J and Lange B (eds). Web-Based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*). http://webdictionary.personalcarecouncil.org/jsp/IngredientSearchPage.jsp. Washington, D.C. Last Updated 2017. Date Accessed 8-29-2017.

2. Boyer IJ, Burnett CL, Heldreth B, et al. Safety Assessment of PEGs Cocamine and Related Ingredients as Used in Cosmetics. *Int J Toxicol*. 2018;37(Suppl 2):10S-60S.

3. Bergfeld WF, Belsito DV, Hill RA, et al. Final Report of the Cosmetic Ingredient Review Expert Panel of the Amended Safety Assessment of Triethylene Glycol and Polyethylene Glycols (PEGs)-4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEGs ≥ 4 as used in Cosmetics. 2010. Available from CIR at https://www.cir-safety.org/ingredients. Available from CIR at https://www.cir-safety.org/ingredients.

4. Fiume MM, Bergfeld WF, Belsito DV, et al. Safety Assessment of Propylene Glycol, Tripropylene Glycol, and PPGs as Used in Cosmetics. *Int J Toxicol*. 2012;31(Suppl 2):245S-260S.

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

6. Fiume MM, Heldreth BA, Bergfeld WF, et al. Safety Assessment of Ethanolamides as Used in Cosmetics. *Int J Toxicol*. 2015;34(Suppl 1):18S-34S.

7. Australian Government Department of Health National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Full Public Report on Promidium CO. File No: NA/908 (Promidium CO is a trade name for PPG-2 Hydroxyethyl Cocamide). 2001. https://www.nicnas.gov.au/search?query=NA%2F908&collection=nicnas-meta. Date Accessed 8-29-2017.

8. Australian Government Department of Health National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Public Report on PEG-4 Rapeseedamide. File No: STD/1443. https://www.nicnas.gov.au/search?query=STD%2F1443&collection=nicnas-meta. Last Updated 2013. Date Accessed 8-29-2017.

9. Australian Government Department of Health National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Full Public Report on Promidium IS. File No: STD/1099 (Promidium IS is also known as PPG-2 hydroxyethyl isostearamide, a component Hydroxyethyl Coco/Isostearamide). https://www.nicnas.gov.au/search?query=STD%2F1099&collection=nicnas-meta. Last Updated 2004. Date Accessed 8-29-2017.

10. Burnett CL, Fiume MM, Bergfeld WF, et al. Safety Assessment of Plant-Derived Fatty Acid Oils. *Int J Toxicol*. 2017;36(Suppl 3):51S-129S. Available from CIR at https://www.cir-safety.org/ingredients.

11. 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. Available from CIR at https://www.cir-safety.org/ingredients.

12. 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.

13. Elder RL (ed). Final Report of the Safety Assessment for Acetylated Lanolin Alcohol and Related Compounds. *J Environ Pathol Toxicol*. 1980;4(4):63-92.

14. 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. Available from CIR at https://www.cir-safety.org/ingredients.

15. Stepan®. Ninol® C-5 (PEG-6 Cocamide). https://www.stepan.com/products/Surfactants/NINOL%C2%AE/NINOL%C2%AE-C-5.aspx. Last Updated 2018. Date Accessed 3-29-2018.

16. Stepan®. Product Bulletin: Ninol® C-5 (PEG-6 Cocamide). https://www.stepan.com/uploadedFiles/Literature_and_Downloads/Product_Bulletins/Surfactants/NINOL%C2%AE/NINOLC5.pdf. Last Updated 2017. Date Accessed 3-29-2018.

17. KAO. Amidet® N Information Brochure. http://www.in-cosmetics.com/__novadocuments/7280. Last Updated 2018. Date Accessed 7-12-2018.

18. Anonymous. 2018. Method of manufacture and impurities PEG-50 Hydrogenated Palmamide. Unpublished data submitted by Personal Care Products Council on October 23, 2018.

19. Anonymous. 2018. Method of manufacture PPG-2 Cocamide. Unpublished data submitted by Personal Care Products Council on November 26, 2018.

20. Anonymous. 2018. Process description PPG-2 Hydroxyethyl Coco/Isostearamide. Unpublished data submitted by Personal Care Products Council on November 20, 2018.

21. KAO. Amidet N brochure. http://chemical.kao.com/us/pdf/catalog/catalog_B0017568.pdf. Last Updated 2014. Date Accessed 7-12-2018.

22. Anonymous. 2018. PPG-2 Hydroxyethyl Cocamide purity and impurities. Unpublished data submitted by Personal Care Products Council on November 20, 2018.

23. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. College Park, MD: 2019. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2019; received February 13, 2019.

24. Personal Care Products Council. 2018. Council Concentration of Use Survey: Updated Use Information Alkoxylated Fatty Amides. Unpublished data submitted by Personal Care Products Council on October 26, 2018.

25. Personal Care Products Council. 2019. Concentration of Use Information: Alkoxylated Fatty Amides Included in the October 2018 Concentration of Use Survey. Unpublished data submitted by the Personal Care Products Council on January 2, 2019.

26. Johnsen MA. The influence of particle size. *Spray Technol Marketing*. 2004;14(11):24-27.

27. Rothe H. Special Aspects of Cosmetic Spray Evalulation. 9-26-2011. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, D.C.

28. Bremmer HJ, Prud'homme de Lodder LCH, and Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. Bilthoven, Netherlands: Netherlands National Institute for Public Health and the Environment. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

29. 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. PM:21669261.

30. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated 2016. Date Accessed 8-29-2017.

31. CIR Science and Support Committee (SSC) of the Personal Care Products Council. 2018. Exposure Assessment: Alkoxylated Fatty Amides. Unpublished data submitted by the Personal Care Products Council on December 3, 2018.

32. KAO Chemicals Europe. Amidet® N. http://www.kaochemicals-eu.com/products/peg-4-rapeseedamide. Last Updated 2018. Date Accessed 7-12-2018.

33. Huntingdon Life Sciences Limited. 1999. Acute dermal toxicity to the rat PPG-2 Hydroxyethyl Cocamide. Unpublished data submitted by the Personal Care Products Council on September 13, 2018.

34. Huntingdon Life Sciences Limited. 1999. Acute skin irritation to the rabbit PPG-2 Hydroxyethyl Cocamide. Unpublished data submitted by Personal Care Products Council oon September 13, 2018.

35. Huntingdon Life Sciences Limited. 1999. Skin sensitization to the guinea pig (Magnusson & Kligman method) PPG-2 Hydroxyethyl Cocamide. Unpublished data submitted by Personal Care Products Council on September 13, 2018.

36. Isaksson M. Occupational allergic contact dermatitis from PEG-4 rapeseed amide in a massage oil. *Contact Dermatitis*. 2002;47(3):175-176. PM:12492561.

2019 VCRP DATA – Alkoxylated Fatty Amides

PEG-2 COCAMIDE	10A - Bath Soaps and Detergents	2
PEG-3 COCAMIDE	12A - Cleansing	1
PEG-3 COCAMIDE	12F - Moisturizing	1
PEG-3 COCAMIDE	12G - Night	1
PEG-4 Cocamide - 0		
PEG-5 COCAMIDE	05F - Shampoos (non-coloring)	2
PEG-5 COCAMIDE	10A - Bath Soaps and Detergents	2
PEG-5 COCAMIDE	10E - Other Personal Cleanliness Products	16
PEG-6 COCAMIDE	05F - Shampoos (non-coloring)	3
PEG-6 COCAMIDE	05I - Other Hair Preparations	1
PEG-6 COCAMIDE	06D - Hair Shampoos (coloring)	4
PEG-6 COCAMIDE	10A - Bath Soaps and Detergents	8
PEG-6 COCAMIDE	12A - Cleansing	1
PEG-6 COCAMIDE	12D - Body and Hand (exc shave)	1
PEG-6 COCAMIDE	12F - Moisturizing	1
PEG-6 COCAMIDE	12G - Night	1
PEG-7 Cocamide - 0		
PEG-11 Cocamide - 0		
PEG-20 Cocamide - 0		
PEG-3 Cocamide DEA - 0		
PEG-20 Cocamide MEA - 0		
PEG-6 Hydrogenated Palmamide - 0		
PEG-50 HYDROGENATED PALMAMIDE	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	20
PEG-50 HYDROGENATED PALMAMIDE	06H - Other Hair Coloring Preparation	6
PEG-13 Hydrogenated Tallow Amide - 0		
PEG-5 Lanolinamide - 0		
PEG-2 Lauramide - 0		
PEG-3 Lauramide - 0 (has conc of use data)		
PEG-5 Lauramide - 0		
PEG-6 Lauramide - 0 (has conc of use data)		
PEG-11 Lauramide - 0		
PEG-3 Oleamide - 0		
PEG-4 Oleamide - 0		
PEG-5 Oleamide - 0		
PEG-6 Oleamide - 0		
PEG-7 Oleamide - 0		
PEG-9 Oleamide - 0		

2019 VCRP DATA – Alkoxylated Fatty Amides

PEG-4 RAPESEEDAMIDE	02B - Bubble Baths	3
PEG-4 RAPESEEDAMIDE	05A - Hair Conditioner	3
PEG-4 RAPESEEDAMIDE	05E - Rinses (non-coloring)	1
PEG-4 RAPESEEDAMIDE	05F - Shampoos (non-coloring)	48
PEG-4 RAPESEEDAMIDE	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
PEG-4 RAPESEEDAMIDE	05I - Other Hair Preparations	1
PEG-4 RAPESEEDAMIDE	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	176
PEG-4 RAPESEEDAMIDE	06H - Other Hair Coloring Preparation	2
PEG-4 RAPESEEDAMIDE	10A - Bath Soaps and Detergents	46
PEG-4 RAPESEEDAMIDE	10C - Douches	3
PEG-4 RAPESEEDAMIDE	10E - Other Personal Cleanliness Products	14
PEG-4 RAPESEEDAMIDE	12J - Other Skin Care Preps	3

PEG-4 Stearamide - 0

PEG-10 Stearamide - 0

PEG-15 Stearamide - 0

PEG-50 Stearamide - 0

PEG-5 Tallow Amide - 0

PEG-8 Tallow Amide - 0

PEG-50 Tallow Amide - 0 (has conc of use data)

Polyglyceryl-4-PEG-2 Cocamide - 0

PPG-2 COCAMIDE	05F - Shampoos (non-coloring)	2
PPG-2 COCAMIDE	12A - Cleansing	1

PPG-1 Hydroxyethyl Caprylamide - 0

PPG-2 HYDROXYETHYL COCAMIDE	01A - Baby Shampoos	1
PPG-2 HYDROXYETHYL COCAMIDE	01C - Other Baby Products	2
PPG-2 HYDROXYETHYL COCAMIDE	02B - Bubble Baths	4
PPG-2 HYDROXYETHYL COCAMIDE	02D - Other Bath Preparations	6
PPG-2 HYDROXYETHYL COCAMIDE	05F - Shampoos (non-coloring)	32
PPG-2 HYDROXYETHYL COCAMIDE	05I - Other Hair Preparations	1
PPG-2 HYDROXYETHYL COCAMIDE	10A - Bath Soaps and Detergents	43
PPG-2 HYDROXYETHYL COCAMIDE	10E - Other Personal Cleanliness Products	238
PPG-2 HYDROXYETHYL COCAMIDE	11E - Shaving Cream	2
PPG-2 HYDROXYETHYL COCAMIDE	12A - Cleansing	22
PPG-2 HYDROXYETHYL COCAMIDE	12F - Moisturizing	1
PPG-2 HYDROXYETHYL COCAMIDE	12J - Other Skin Care Preps	2

PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	05F - Shampoos (non-coloring)	11
PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	1
PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	10A - Bath Soaps and Detergents	4
PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	10E - Other Personal Cleanliness Products	2
PPG-2 HYDROXYETHYL COCO/ISOSTEARAMIDE	12A - Cleansing	8

PPG-3 Hydroxyethyl Soyamide - 0

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: January 2, 2019

SUBJECT: Concentration of Use Information: Alkoxylated Fatty Amides Included in the October 2018 Concentration of Use Survey

Concentration of Use – Additional Alkoxylated Fatty Amides*

PEG-3 Lauramide
PEG-20 Cocamide MEA

Ingredient	Product Category	Maximum Concentration of Use
PEG-3 Lauramide	Shampoos (noncoloring)	4%

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

Information collected in 2018
Table prepared January 2, 2019

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: December 3, 2018

SUBJECT: Exposure Assessment: Alkoxylated Fatty Amides

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to comment on the draft report on the alkoxylated fatty amides.

Alkoxylated fatty amides are surfactants that are used primarily in rinse-off products and hair products. The only leave-on dermal use reported in the Council concentration of use survey is 0.35% PPG-2 Hydroxyethyl Cocamide in face and neck products. Based on the surfactant function, and the reported pattern of use, the CIR SSC considers that the existing studies summarized in the CIR report support the safe use of these ingredients with a conclusion of safe when formulated to be non-irritating.

This conclusion would be consistent with Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) which used the available data to support the requested personal care product uses of PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide. NICNAS[1] identified a NOAEL of 150 mg/kg/day for PEG-4 Rapeseedamide from a 28-day study in rats for the basis of their risk assessment for use of this ingredient in cosmetic products. The effects observed at 150 mg/kg/day (forestomach irritation) were considered minimal. This NOAEL is further supported by a screening reproductive and developmental toxicity study (OECD 421) in rats of PEG-4 Rapeseedamide in which the NOAEL was 500 mg/kg/day. NICNAS estimated exposure of 1.38 mg/kg/day from use of makeup remover, shower gel, hand wash soap, shampoo, hair conditioner and facial cleanser - all containing 8% PEG-4 Rapeseedamide. They also estimated hair dye exposure of 0.1 mg/kg/day for a hair dye containing 15% PEG-4 Rapeseedamide. NICNAS estimated a total exposure of 1.48 mg/kg/day (Margin of Exposure (MOE)= 150/1.48 = 101), which they considered acceptable. The exposure concentrations used by NICNAS are higher than found in the Council concentration of use

[1] https://www.nicnas.gov.au/search?query=STD%2F1443&collection=nicnas-meta

survey e.g., the Council maximum use concentration in bath soaps and detergents was 4% and in hair dyes and colors was 9.3%.

This NICNAS exposure assessment should be described in the CIR report.

For PPG-2 Hydroxyethyl Cocamide, NICNAS[2] identified a NOAEL of 1000 mg/kg/day, in a 28-day oral study in rats. This dose and the 150 mg/kg/day dose were associated with urinary potassium decreases but no histopathological changes. NICNAS concluded that use of shampoos containing 4% of PPG-2 Hydroxyethyl Cocamide was not likely to pose a significant threat to public health.

NICNAS did not consider the safety of dermal leave-on products. Assuming the 95th percentile use of face lotion[3] (3.99 g/day), the estimated exposure to PPG-2 Hydroxyethyl Cocamide from use in a face product containing 0.35% is 0.24 mg/kg/day. Applying default assumptions from the SCCS Notes of Guidance[4] for leave-on hair products (5.74 mg/kg/day), the estimated exposure to PPG-2 Hydroxyethyl Cocamide from use in a hair styling product containing 7.5% is 0.43 mg/kg/day. Both of these values are sufficiently below the lower NOAEL for this group of ingredients (150 mg/kg/day), e.g., MOE of 625 for the face product, MOE of 349 for the hair styling product, to be considered safe.

Therefore, based on the conservative assumption that all of the alkoxylated fatty amide in a cosmetic product will be absorbed, estimated exposure is lower than the 150 mg/kg/day systemic oral NOAEL. This suggests that additional dermal absorption data on PPG-2 Hydroxyethyl Cocamide and PEG-3 Rapeseedamide are not needed to address potential concerns regarding systemic toxicity.

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[2]https://www.nicnas.gov.au/search?query=NA%2F908&collection=nicnas-meta

[3]Loretz LJ, Api AM, Barraj LM, et al. 2005. Exposure data for cosmetic products: lipstick, body lotion and face cream. *Fd Chem Toxicol* 43(2): 279-291.

[4]Scientific Committee on Consumer Safety (SCCS). 2018. The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation 10th revision.

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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: November 28, 2018

SUBJECT: Draft Tentative Report: Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics (draft prepared for the December 3-4, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics.

Key Issues

It is not clear why PEG-5 Oleamide Dioleate was removed from the report and PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA were left in the report as all three ingredients have three carbon chains bound to the nitrogen (see Figure 2 in the report). With PEG-3 Cocamide DEA and PEG-2 Tallowamide DEA in the report, all of the other ingredients in the report are not "secondary amides exclusively", as stated in the memo.

The maximum concentration of use of PPG-2 Hydroxyethyl Cocamide in leave-on dermal products changed from 3% in body and hand products to 0.35% in face and neck products. Although this change is reflected in Table 4, it has not been corrected in the Cosmetic Use section or the Summary. Not only has the use concentration gone down, the change in the amount of product used in body products compared to face products is significant.

The NICNAS risk assessment for the use of PEG-4 Rapeseedamide in cosmetics should be added to the CIR report.

Additional Considerations

Introduction; Discussion - Reference 5 is the CIR report on Diethanolamides. It is not clear why the ingredients in this report are being called "polyalkoxylated ethanolamides" in both the Introduction and the Discussion. The ingredients in the CIR report on Diethanolamides were not "polyalkoxylated".

Short-Term, Oral, PEG-4 Rapeseedamide - It should also be stated that NICNAS did not

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consider the forestomach effects to be significant and used the 150 mg/kg/day dose in their calculation of a margin of exposure.

DART, PEG-4 Rapeseedamide - Please correct the doses from: "0, 15, 15 or 500" to "0, 15, 150 or 500"

Summary - Please correct: "orals studies"

Discussion - Please correct: "the dangers risks"

Reference 2 - As the CIR report on PEGs Cocamine has now been published, reference 2 needs to be updated.

Table 3 - Rather than 2.6, NICNAS indicates that the log K_{ow} for PEG-Rapeseedamide is >2.56. It also stated that this ingredient is expected to partition to surface boundaries. For PPG-2 Hydroxyethyl Cocamide, NICNAS states that the high variability of the log K_{ow} was due the surfactant nature of the ingredient. This information should be added to Table 3.

The Summary states: "The NOAEL for developmental effects in the pups was 180 mg/kg bw/day." Where did this come from as it is not stated earlier in the report.

Uterotrophic assays are not *in vitro* studies as stated in the Summary.

Please correct "Harley" albino guinea pigs

References are generally not included in the Summary (a 6 is in the paragraph on human sensitization studies).

Table 3 - This table should indicate the NESIL on which the IFRA limits were developed.

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Personal Care Products Council
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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: January 11, 2019

SUBJECT: Tentative Report: Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics (release date: January 2, 2019

The Council respectfully submits the following comments on the tentative report, Safety Assessment of Alkoxylated Fatty Amides as Used in Cosmetics.

Key Issues

The internet Chemistry Dictionary (https://chemdictionary.org/amide/) defines an amide and simple amide as: "Amides ($RCONH_2$) are functional group where carbonyl group attached to a amine group. In simple amides nitrogen attached with two hydrogen atoms." This is also supported by this website https://www.chemguide.co.uk/organicprops/amides/background.html in which the examples of "simple" amides all have the NH_2 group. Because none of the ingredients in this report have a nitrogen bound to two hydrogens, is it correct to call the ingredients in this report "simple" amides as stated in the Abstract, Introduction, Chemistry, Summary and Discussion sections?

As the method of manufacture indicates, and as stated in the NICNAS assessment for Promidium IS (reference 9), PPG-2 hydroxyethyl isostearamide is a component of the material given the INCI name PPG-2 Hydroethyl Coco/Isostearamide. Therefore, rather than stating that PPG-2 hydroxyethyl isostearamide is not a cosmetic ingredient and that information on it is provided for read-across, it should be stated that PPG-2 hydroxyethyl isostearamide is a component of a cosmetic ingredient. This needs to be corrected in the following sections in the CIR report: Acute Toxicity, Genotoxicity, Summary, Table 6, Table 7 and reference 9.

As PPG-2 hydroxyethyl isostearamide is a component of PPG-2 Hydroxyethyl Coco/Isostearamide, the physical and chemical properties included in the NICNAS assessment (reference 9) should be added to Table 3.

Additional Considerations

Introduction - As the NICNAS assessments cited in this report consider exposure, the assessments do not just concern "hazard". The assessments should be called hazard and risk assessments (or just call them NICNAS assessments).

Impurities, PEG-4 Rapeseedamide - It should be noted that 92-93% active matter was reported in sales information prepared for the cosmetics industry. The purity of 60-80% reported by NICNAS included a trade name that is marketed for use in metal working fluids.

Non-Cosmetic Use - It should also be noted that the NICNAS assessment (reference 8) indicates that PEG-4 Rapeseedamide is also used as an additive in metal working fluids and photochemicals.

Exposure Assessment, PEG-4 Rapeseedamide - The 150 mg/kg bw/day was an actual dose that was tested. It should not state that "the NOAEL that was calculated for female rats...". The NOAEL was not "calculated".

Ocular Irritation, PEG-4 Rapeseedamide - The study was completed using OECD TG 405 which specifies a dose volume of 0.1 ml. Therefore, it is not necessary to state: "(The volume instilled was not specified.)".

Summary - In the paragraph summarizing the risk assessment, it should be made clear that NICNAS calculated a MOE of 101 using product concentrations greater than reported in the Council concentration of use survey.

Discussion - Do the oral systemic toxicity studies really mitigate concerns regarding "dermal toxicity", or do these studies mitigate concerns regarding "systemic toxicity following dermal exposure"?