BLUE

Ethanolamides

CIR EXPERT PANEL MEETING

MARCH 5-6, 2012

Cosmetic Ingredient Review
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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Monice M. Fiume MMF
Senior Scientific Analyst/Writer

Date: February 10, 2012

Subject: (Draft) Final Amended Safety Assessment on Ethanolamides as Used in Cosmetics

Enclosed is the draft final amended safety assessment on ethanolamides. This assessment was initiated as a re-review of isostearamide MEA, myristamide MEA, and stearamide MEA. At the December 2011 meeting, the Panel confirmed that the safety of a group of 25 chemically related ethanolamides also was supported by the available data in this safety assessment.

Accordingly, the Panel issued a tentative amended safety assessment on 28 ethanolamides (original 3 in the re-review + 25 additional ethanolamides) with the conclusion that these ingredients are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating. The Expert Panel cautioned that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

It is expected that the Panel will issue a final amended safety assessment at this meeting.

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Ethanolamides

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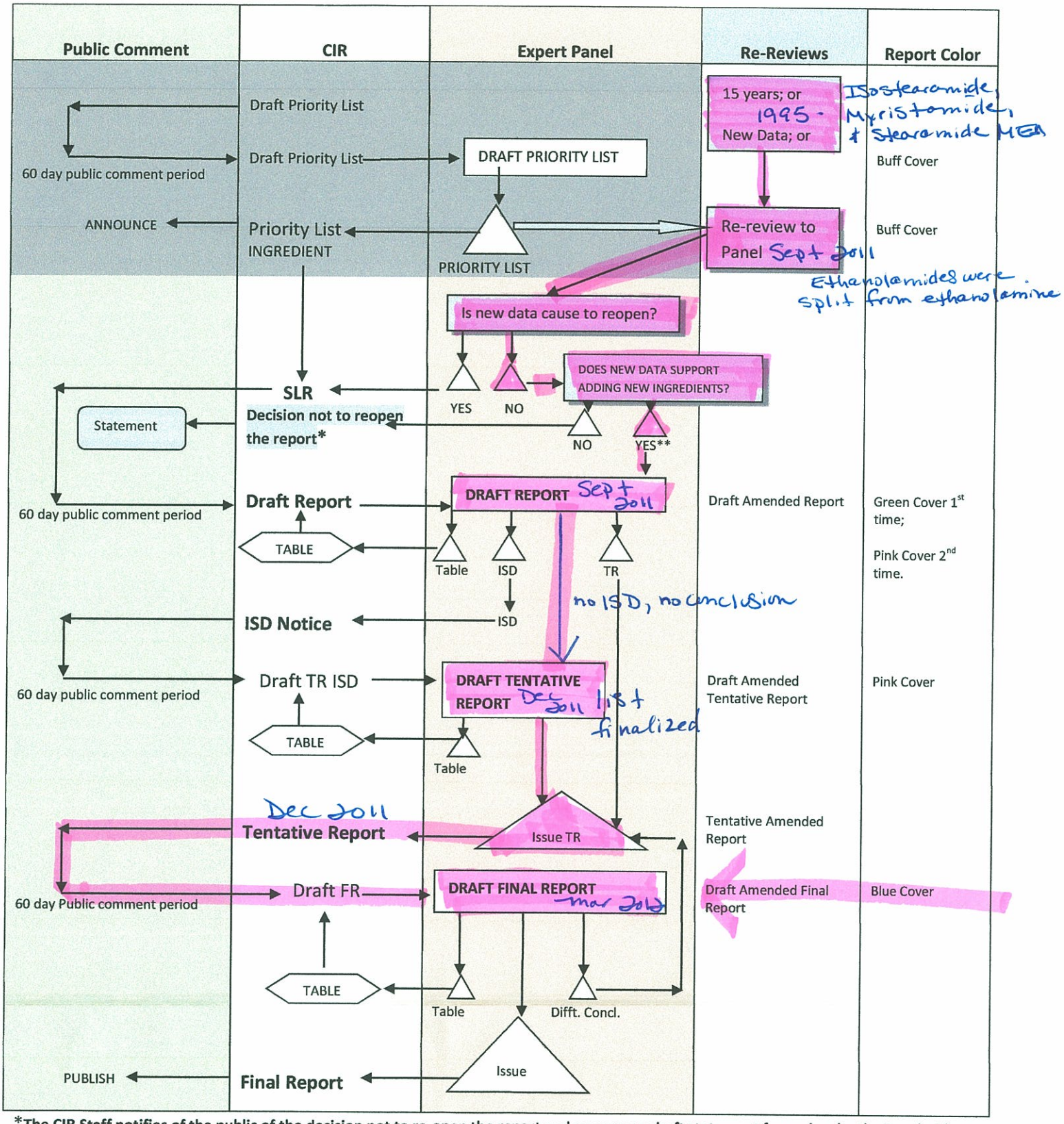
SAFETY ASSESSMENT FLOW CHART

March 2012



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision

▭ Document for Panel Review

⇨ Option for Re-review

History: Ethanolamides

September 26-27, 2011: Question of Re-Review
A Draft Amended Safety Assessment was presented to the Panel on Ethanolamine, and it included a section on ethanolamides. The Panel was asked whether the Ethanolamides should be re-reviewed and was it appropriate to include these ingredients in this report or look at them separately.

The Panel decided that it was appropriate to re-review these ingredients, but that they should be reviewed in a separate report. The Panel also stated that inclusion of the Glycol Ethers was appropriate. No proposed add-ons were deleted from the report.

December 12-13, 2011: (Draft) Tentative Amended Safety Assessment
The draft Tentative Amended Report on Ethanolamides was presented to the Panel. No new data were received since the September meeting.

At this meeting, 22 ingredients were deleted from the re-review, leaving a total of 28 ingredients in this review. Also, the Panel issued (by a 7-1 vote) a Tentative Amended Safety Assessment with a conclusion of safe as used when formulated to be non-irritating. These ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

March 5-6, 2012: (Draft) Final Amended Safety Assessment
Minor comments were received from the Council and addressed.

Ethanolamides Data Profile* March 2012 – Writer, Monice Fiume

	Previously Reviewed*	CIR Review Substituent*	Reported Use	Info on Free MEA Content	log P value	Toxicokinetics Data	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Dermal	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhalation	Repro/Dev Tox**	Genotoxicity	Carc.	Dermal Irr/Sens	Ocular Irritation
Acetamide MEA	1993		x	x	x		x	x		x				x		x	x
Azelamide MEA		2010															
Babassuamide MEA		2011															
Behenamide MEA					x												
C16-22 Acid Amide MEA					x												
Cocamide MEA	1999	1986;2011	x				x	x		x	x			x		x	
Cocamide Methyl MEA		2011	x														
Cocamidopropyl Betainamide MEA Chloride		2010	x														
Hydroxystearamide MEA		1999			x												
Isostearamide MEA	1995	1983															
Lactamide MEA		1998	x														
Lauramide MEA		1987	x		x			x						x		x	x
Linoleamide MEA					x												
Myristamide MEA	1995	1987	x	x	x												
Oatamide MEA		2011			x												
Oleamide MEA		1987															
Oliveamide MEA		2011															
Palm Kernelamide MEA		2000;2011															
Palmamide MEA		2000;2011															
Palmitamide MEA		1987			x												
Pantothenamide MEA		1987															
Peanutamide MEA		2001;2011	x														
Ricinoleamide MEA		2007	x		x												
Stearamide MEA	1995	1987	x	x	x					x						x	x
Sunfloweramide MEA		2011															
Tallowamide MEA																	
Trideceth-2 Carboxamide MEA		2010	x														
Undecylenamide MEA			x		x												
Substituents																	
Ethanolamine		2011				x	x	x	x	x	x	x	x	x		x	x
Arachis Hypogaea (Peanut) Oil		2001;2011				x					x			x	x	x	x
Avena Sativa (Oat) Kernel Oil		2011														x	
Azelaic Acid		2010				x		x			x		x	x		x	
Cocamidopropyl Betaine		2010					x	x			x			x	x	x	x
Coconut Acid		1986;2011														x	x
Elaeis Guineensis (Palm) Kernel Oil		2000;2011				x					x		x		x	x	
Elaeis Guineensis (Palm) Oil		2000;2011						x			x		x	x	x	x	x
Helianthus Annuus (Sunflower) Seed Oil		2011														x	
Hydroxystearic Acid		1999				x					x		x	x	x	x	

Ethanolamides Data Profile* March 2012 – Writer, Monice Fiume

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Isostearic Acid		1983				x		x								x	x
Lactic Acid		1998				x		x		x	x		x	x	x	x	x
Lauric Acid		1987						x		x				x	x	x	x
Myristic Acid		1987						x		x						x	x
Olea Europaea (Olive) Fruit Oil		2011														x	x
Oleic Acid		1987				x	x	x		x	x			x	x	x	x
Orbignya Oleifera (Babassu) Oil		2011														x	
Palmitic Acid		1987				x	x			x					x	x	x
Pantothenic Acid		1987				x		x		x	x					x	x
PEGs		2010				x	x	x		x	x	x	x	x	x	x	x
Ricinoleic Acid		2007				x		x							x	x	
Stearic Acid		1987				x	x	x		x	x			x	x	x	x
Trideceth-2		2010															

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

*year of review is provided

**data on the DEA amides were not available; data from previous CIR reports on DEA and fatty acids were summarized

ETHANOLAMIDES SEARCH STRATEGY – SCIFINDER – originally searched June 10, 2011

12/12/2011 – searched (ethanolamine OR ethanolamide OR MEA or monoethanolamine) AND carcinogenicity – 0 useful hits
searched for repro tox – 0 hits
searched lipases amides and skin ad 'lipases convert amides'

Keep Me Posted Results updates are received weekly

Ethanolamides alone were searched for a Keep Me Posted file:
142-26-7; 109-83-1; 68140-00-1; 54536-43-5; 111-57-9; azelamide MEA; 69227-24-3; 94109-05-4; C16-22 Acid Amide MEA; Cocamide MEthyl MEA; 164288-56-6; Deoxyphytantriyl Palmitamide MEA; 884905-11-7; 934175-85-6; hydroxyethyl pantothenamide MEA; hydroxypropyl bisisostearamide MEA; hydroxypropyl bislauramide MEA; hydroxypropyl bispalmitamide MEA; hydroxypropyl bisstearamide MEA; 106-15-0; 5422-34-4; 142-78-9; 10015-67-5; myristoyl/palmitoyl oxostearamide/arachamide; oatamide MEA
111-58-0; oliveamide MEA; palm kernelamide MEA; palmamide MEA; 544-31-0; pantothenamide MEA; peanutamide MEA; 106-16-1; 75033-33-9; 14351-40-7; 141-21-9; 69227-24-3; 68440-25-5; 107628-04-6; 20545-92-0; 75046-17-2; 61791-08-0

Initially searched with ethanolamine

1. Searched all ingredients (except MEA) with CAS #s (38 substances) – **18,866 references**
    a. Refined by document type – **7091 references**
    b. Refined by removing documents in Chinese – **5701 references**
2. Searched MEA by CAS #
    a. Refined by document type – **14229 references**
    b. Refined by year 1980+ - **11440 references**
3. Combined results of SS 1 and 2 above - **18968 references**
4. Searched all ingredients without CAS #, refined by document type
    a. MEA laureth carboxylate – **1**
    b. MEA steareth carboxylate – **0**
    c. MEA talloweth – **0**
    d. MEA hydrolyzed Silk – **0**
    e. MEA hydrolyzed collagen – **1**
    f. MEA distearyl phosphate – **0**
    g. Butylethanolamine – **128**
    h. Stearamidoethyl ethanolamine phosphate - **0**
    i. Lysophosphatidylethanolamine – **1982**
    j. Azelamide MEA – **0**
    k. Cocamide methyl MEA – **0**
    l. Deoxyphytantriyl Palmitamide MEA – **0**
    m. Hydroxyethyl pantotheamide – **0**
    n. Hydroxylpropyl MEA – **227**
    o. Myristoyl/palmitoyl/oxostearamide/arachamide DEA – **0**
    p. Oatamide MEA – **0**
    q. Palm kernelamide MEA – **0**
    r. Palmamide MEA – **0**
    s. Panthothenamide MEA – **0**
    t. Peanutamide MEA – **0**
    u. PEG Cocamide MEA – **0**
5. Combined SS 3 and all results of SS 4 – **18413 references**
6. Applied the following qualifiers to SS 5 above
    a. Carcinogen – **593**
    b. Mutagen – **79**
    c. Teratogen – **15**
    d. Developmental toxicity – **56**
    e. Reproductive toxicity – **8**
    f. Dermal – **46**
    g. Toxicology – **728**
    h. Ocular – **164**
    i. Irritation – **86**

j. Sensitization – **119**
k. Photosensitization – **59**
l. ADME – **7**
m. Dermal absoroption – **4**
n. Excretion – **70**
o. Pharmacokinetics – **116**
p. Kidney renal – **219**
q. Choline deficiency – **20**
r. Nitrosation – **53**

7. Combined all of SS 6 – **2032 references**

SEARCH STRATEGY – TEA/DEA/MEA

	TOXLINE	PUBMED	EU
Jan 17. 2010			
DEA			not to be used
111-42-2 & choline	13	15	
111-42-2 & carcinogen*	83	21	
choline & deficiency & human & cancer	38		
TEA			restrictions
102-71-6 & carcinogen*	55	11	
102-71-6 & choline	5	2	
MEA			restrictions
Jan 25, 2010			
102-71-6 OR 111-42-2 (1980-current)	1003 (downloaded 58)		

UPDATED SEARCH May 31, 2010

(102-71-6 OR 111-42-2 OR 141-43-5) AND (REPRODUCTI* OR TERATOGEN*) – 142 (Toxline); 41 (DART)

(102-71-6 OR 111-42-2 OR 141-43-5) AND (DEVELOPMENT* OR FETOTOX*) – 378 (Toxline); 47 (DART)

(102-71-6 OR 111-42-2 OR 141-43-5) AND TOX*

(102-71-6 OR 111-42-2 OR 141-43-5) AND (GENOTOX* OR MUTAGEN* OR CLASTOGEN*) – 286 Toxline); 7 (DART); 9 (CCRIS)

(102-71-6 OR 111-42-2 OR 141-43-5) AND (SENSITIZA* OR SENSITIZE* OR SENSITIS* OR IRRIT*) – 306 (Toxline); 6 (DART)

(102-71-6 OR 111-42-2 OR 141-43-5) AND (METBOLI* OR ABSORB* OR ABSORP* OR DISTRIBUT* OR EXCRET*) – 403 (Toxline); 18 (DART)

141-43-5 AND CARCINOGEN* – 193

141-43-4 AND CHOLINE - 0

Total Download (most duplicates removed): 1218

UPDATED SEARCH – Sept 21, 2010 – last 12 mos

102-71-8 OR 111-42-2 OR 141-43-5 128 hits/1 useful

Minutes

DR. BELSITO: What? Okay. So now we're moving to ethanolamide. So, in September, again, we came up with a list of specific ethanolamides to be included. And it follows the same pattern that we did with DEA. And this looks pretty good.

I guess I have one question: Where did sodium MEA/PEG3 cocamide sulfate come from? That was not in the list last go around -- at least, not in my Panel Book.

MS. FIUME: It probably should have been. And we've added it back. Bart, do you remember what happenedI'm sorry, it was supposed to be in the list, and now has been added back in?

DR. BELSITO: Okay. Dan, you're okay with that one?

DR. LIEBLER: Which one?

DR. BELSITO: Sodium MEA/PEG3 cocamide sulfate.

DR. LIEBLER: Let me take a quick look.

DR. ANDERSEN: Panel Book page 30.

DR. LIEBLER: Oh, page 30, okay..

DR. ANDERSEN: And it's a (inaudible) propylene glycol, not a polyethylene glycol.

MS. FIUME: No, it's actually a polyethylene glycol. On page 17 it's listed. Panel Book page 17 has it listed correctly.

DR. LIEBLER: So, on the table, it's wrong?

MS. FIUME: It's a typo.

DR. LIEBLER: Okay. I guess in this list of ingredients it's a bit of an oddball, because it's a sulfate ester -- I'm scrolling through to upload this into my brain, here. But I don't see any other sulfate esters.

I'm not sure that that's a problem. I mean, the alkyl sulfates all have been reviewed previously -- right?

MS. FIUME: Yes.

DR. BELSITO: But is this -- okay. Just asking.

MS. FIUME: This report hasn't gone tentative yet, so.

DR. LIEBLER: Yeah, I have another one, actually, I wanted to pull, or suggest we pull out. This one, I hadn't spotted it, you know, it does have the ethanolamide functional moiety in it. The sulfate part makes it a little different than most of the other ingredients -- not different enough that I would have concern about it, though, about it being -- I guess these would be a little bit more polar, but then they've got these big alkyl chains.

I guess I'm not concerned about that. I could go either way on that one. I'm feeling very wishy-washy today, by the way. Sorry about that. I need some more coffee.

The one I had concern about was on the bottom of Panel Book 26, the cocamidopropyl betainamide MEA chloride. This one really is kind of different. It's got that quaternary amine in the side chain. It's beta to the amide linkage.

DR. BELSITO: I've looked at cocamidopropyl betain, and found that safe as used.

DR. LIEBLER: Uh-huh.

DR. BELSITO: So, is there something about the linkage that bothers you?

DR. LIEBLER: No, I just think it's more -- it's not an issue of safety, it's more an issue of sort of chemical similarity, does it belong in this group?

DR. BELSITO: I mean, that's the nature of cocamidopropyl betain, though, as a quarternary ammonium.

DR. LIEBLER: Right. Right, it's just an ethanolamine amide --

DR. BELSITO: That happens to be of a quarternary amine. Well, again, I'm not the chemist. I'm just saying that, in this particular case, we've reviewed both sides. And unless you see some issue with the linkage --

DR. LIEBLER: No, I don't think so. I just was thinking that it's chemically dissimilar. But, actually, it's used for some of the same things. I withdraw my concern about it.

DR. BELSITO: Linda?

DR. KATZ: Actually, we had a similar kind of indirect concern with some of the, I guess, larger groups, where the linkages may not be quite so apparent.

And do you need something to sort of explain why they're being linked together? Which raises part of the question that you're having the discussion here now.

But for someone who's not privy to the discussion, would they be able to figure out why they were linked? And does there need to be some kind of a footnote, or just something, to say why things are being linked -- if they don't look, on face, like they should be?

DR. BELSITO: So, actually, in the introduction, perhaps, a little bit more reason why the Panel felt that in this case the 47 additional ingredients listed below could be incorporated to our re-review of isostearamide MEA, et cetera.

And, you know, again to the point that we've reviewed what we've reviewed, et cetera.

DR. ANDERSEN: I think --

DR. BELSITO: They have functional similarity, and the structure-activity relationships being similar. We've reviewed safety of these parent compounds. Therefore, the Panel felt comfortable using read-across data to support the entire family.

That probably should be pretty much in everything, except when we take an acid and look at the calcium, sodium, and potassium salts of it, which I don't think most people would have a problem at all..

DR. LIEBLER: I'm not concerned so much -- I'm not focusing, really, on the safety issue here. I'm really focusing on sort of the logic of including these ingredients within the chemical space, you know, within this set of ingredients.

DR. BELSITO: Well, that's what Linda's asking.

DR. KATZ: Yeah.

DR. BELSITO: And making that clear to the reader, why we did that.

DR. LIEBLER: Right, and so if it's been reviewed previously, and it's safe, that still doesn't address the chemistry issue: does it belong in this group? It doesn't matter if it's safe or not. Just does it belong in this group?

And I guess with these compounds, you know, for many of these things where they are long chains, alkyl chains or long-chain polyethoxy chains, those actually dominate the chemistry much more than the ethanolamide part, or the alkanolamide part.

And that's probably reason enough that I don't -- I guess I don't object to the sodium MEA-PPG3 cocamide sulfate. And I suppose, by the same logic, I would be okay with the cocamide with the betain derivative.

But at first glance, it just looks a little dissimilar, chemically. But I think if you consider -- you know, if you consider the entire structure, and you consider its use, it actually does belong in this group.

So, I think that I could help with a little language in the introduction, if there's a question, Monice, to justify inclusion of these. And this may come up in discussion tomorrow.

DR. BELSITO: Perfect.

DR. LIEBLER: And we'll do our best.

DR. BERGFELD: I think you'd probably need a line, also, in your discussion --

DR. LIEBLER: Yes.

DR. BERGFELD: -- just to bring it back to focus.

DR. BELSITO: Okay, but otherwise I think Monice did a very good job with the discussion. And going ahead with a "safe as used."

Any other comments on the ethanolamides?

DR. SNYDER: Yes, I had a couple. So, would it be beneficial to the report to have a more expanded discussion of why we chose to split the reports?

DR. BELSITO: No. (Laughter)

DR. SNYDER: Okay. Okay.

DR. BELSITO: I mean, I don't think -- I mean, we've got enough in the discussion. The reports have been split, you know. They can capture -- anyone interested in that can capture them from the public meetings, records of the meetings when we decided to split them.

But Rachel had a comment?

MS. WEINTRAUB: Yes, I had a comment. So, in my review of this report, I noticed that there was no heading of "Carcinogenicity." And perhaps it was subsumed in another category? But I didn't see it.

And I also noted, in reading the previous report, there was a mention of an "NTP study on DEA" that was being written in 1994, the conclusion was not yet available? And I didn't see a reference to that study nor what the conclusion ultimately was.

So, I wanted the Panel to discuss its relevancy. And if it's not relevant, then the current report would be okay. But if it is, then I think it should be reflected.

MS. FIUME: I apologize that there's not a Carcinogenicity heading in there. That is a complete oversight. And I apologize for that.

The DEA report, I believe, is not as -- when you say "the previous report," are you talking --

MS. WEINTRAUB: Yes. Sorry.

MS. FIUME: -- diethanolamine?

MS. WEINTRAUB: Yes, the report that's in the back. It's one of the two reports that's in the data section on this and I just noted -- I marked it somewhere. It's in one of the two. Yeah, so it's CIR Panel Book page 49 and page 9 of that first report, which includes the carcinogenicity section, as well as the carcinogenesis bioassay being conducted.

DR. BELSITO: Yes, that was for TEA and DEA.

MS. WEINTRAUB: DEA, right.

DR. BELSITO: Right. So we're on MEA.

MS. WEINTRAUB: Yeah. So is it not relevant at all, then?

For this?

DR. BELSITO: I don't -- you know, we don't have the data on MEA.

MS. FIUME: I believe there are no --

DR. BELSITO: Right.

MS. FIUME: I will double-check and do another search tonight. I believe there are no carcinogenicity data on MEA.

MS. WEINTRAUB: Okay.

MS. FIUME: It's my understanding that the DEA information would only be relevant if there was a very high level of DEA in MEA..

It was relevant in the TEA report, because there were higher levels as an impurity. But I don't believe that's the case in the MEA report, unless I'm recollecting incorrectly.

MS. WEINTRAUB: Okay.

DR. ANDERSEN: What we're faced with is an uncertainty about the diethanolamine levels in the mono- ethanolamines. So that's a small red flag.

But I think maybe the point is to not mention the body of work on DEA is probably not good.

DR. BELSITO: Right.

DR. ANDERSEN: If only in the introduction, or someplace, we need to acknowledge that there is a body of work on DEA carcinogenesis, and that that NTP study is now finished, along with substantial follow up on mode of action, yadda, yadda, yadda, to suggest that direct chemical carcinogenesis isn't the issue, but may be a metabolic phenomenon.

DR. BELSITO: But you would put that in the MEA report? Or, now, ethanolamine?

DR. ANDERSEN: Well, I think --

DR. BELSITO: We've got -- granted, we don't have any mammalian studies, but we have four, you know, negative Ames tests in, you know, acetamide, cocamide and lauramide MEA. We have no --

DR. ANDERSEN: I was thinking more for the introduction, to simply inform the reader that there is this other body of work. And that its relevance to this report relates to the question of --

DR. BELSITO: DEA contamination..

DR. ANDERSEN: -- small levels of DEA contamination.

DR. LIEBLER: I agree.

DR. BELSITO: Okay.

DR. ANDERSEN: And if -- yeah, I agree with that. I think that since we're going to invoke the DEA issue via the boilerplate in the discussion, we should refer to the body of work on DEA, at least briefly, in the introduction.

DR. BELSITO: Okay.

DR. KLAASSEN: And it maybe needs to be in the discussion, as well, you know, by putting it together with the lack of mutagenicity, et cetera.

This is a concern of this class of compounds, and I think we need to discuss it. It can be a short paragraph. We don't want to overdo it.

DR. ANDERSEN: I get your point. If we're willing to put a sentence in the discussion, as the draft Monice prepared does, that says for the diethanolamine report, "Concerned with levels of free diethanolamine that could be present." Well, why are you concerned?

Well, there's two reasons. One is the question of that body of work on DEA carcinogenesis, which is probably resolved. But the reader ought to know that.

And then the question of the ability of that chemical to form nitrosamines.

I think we can get both in there.

MS. FIUME: Okay. So the DEA is relevant for the ethanolamine report, but not the ethanolamides. Is that correct?

DR. BELSITO: No, I'm hearing it's relevant in both.

MS. FIUME: Because right now, right now there's no reference to DEA impurities in the ethanolamide report.

DR. BELSITO: Well, your discussion, though, does.

MS. FIUME: Ethanolamine.

DR. BELSITO: "Ethanolamides consist of covalent secondary amides. The Panel was concerned that secondary amides tend to react with nitrosating agents to form nitrosamides. Because of the potential for this process to occur, ethanolamides should not be used in cosmetic products in which n-nitroso compounds can be formed."

MS. FIUME: Oh, I'm sorry.

DR. BELSITO: So it's already there in the discussion. And I think, you know, what we're asking for is a little bit about DEA contamination in the introduction, and more of an -- I mean, basically, "safe as used." We like your discussion. And a little bit more explanation of the grouping in both the introduction and the discussion. And a little bit about the potential for DEA contamination in the introduction.

I think the discussion already has that well covered.

DR. LIEBLER: Right. And I think that applies to both the ethanolamides report, and the ethanolamines report. That same little bit in the introduction about the DEA contamination is relevant.

DR. BERGFELD: I'd like to make a point that read- across is okay for us to say, but not okay to go in print. You have to describe what you're actually looking at.

DR. KLAASSEN: You need the words.

DR. BERGFELD: Yeah.

DR. ANDERSEN: Message received..

DR. SNYDER: I had a couple of comments. One is on page 7, the second paragraph -- the first sentence of the second paragraph of the summary.

DR. BELSITO: Page 7, Panel Book, or --

DR. SNYDER: Yes, Panel Book, page 23, 7 of the report, the summary, second paragraph, regarding the amidases.

So, is there a reference for that? Because in the first sentence you say, "Amidases may be present in human skin," and then we go on to say that the activity of that is unknown, both in the next sentence, and then also in the discussion. And I was particularly concerned about in the discussion, when we use the terms in the discussion saying that ethanolamine "may be present" and "might convert."

So I think there's a little bit too many ambiguities there. So I think we need to tighten that up a little bit.

So if there is a reference, and we know the activity, and potential for converting.

MS. FIUME: Bart, do you remember, do we have the reference for that?

MR. HELDRETH: We just have a reference that makes a brash statement. It's not giving actual numbers of activities.

DR. SNYDER: And then I have some comments written in the book regarding the absence of data. Because I think the discussion has to address the absence of the absorption and distribution in metabolism and excretion. Absence of that data, and also the absence of other data that are -- like the reproductive data.

And so I think you've kind of captured that, but I think we need to be a little bit more direct in how we're using that information from other reports to not raise any safety concerns with this report. And so I think we need to just expand on that just a little bit more. And I've captured some of that in my book.

DR. BELSITO: Okay. Any other comments? Monice, you have all that down?

MS. FIUME: I have everybody's book that I'm supposed to check. (Laughter)

Ethanolamides –Marks Team – Dec 12, 2011

DR. MARKS: The next Pink Book is the ethanolamides. And at the September meeting we reopened the safety assessment and added a number of ingredients. So page 17. We have a list of the ingredients. That's Panel Book page 17. Are we happy with all those ingredients as listed?

DR. HILL: No. I'm trying to figure out how some of those got in there.

DR. MARKS: That's why I asked the question.

DR. HILL: This is the first time we've seen the mono - mono ethanolamine amides group after splitting, correct?

MS. FIUME: It came last time and split into two reports under one cover.

DR. MARKS: Right. And we really --

DR. HILL: Right.

DR. MARKS: And we really didn't address these. We just decided to split them out and now we're seeing it. So that's why I brought as the first issue is do we like all these ingredients that are grouped together on page 17?

DR. HILL: Maybe we didn't discuss them but I think I marked a bunch of these in the last book. I thought we had had a discussion about that but apparently not because they're all still in there.

DR. MARKS: So the isostearamide MEA, myristamide MEA, and stearamide MEA were reviewed by the expert panel in '95. And it was concluded these were safe for use in rinse- off products. And then there was a limit placed on leave-on products to have no more than 5 percent free ethanolamine. But the maximum concentration, 17 percent for the isostearamide, myristamide and the stearamide MEA.

So, the following additional 47 ingredients are being included in a re-review of isostearamide, myristamide, and stearamide MEA. So Ron, you immediately said I don't know this list..

DR. HILL: No, I don't.

DR. MARKS: So can we pair down some or did you want to add more?

DR. HILL: We have data that would allow us to read- across on simple MEA amides and when I say simple, I mean that can be fairly elaborated on the left. But some of these are not MEA amides at all. So if you wanted to look at the table of structures I can tell you which -- I mean, basically starting on page 27 because there's a lot on the next page that should certainly be kept. Everything on Panel Book page 27 ought to get out of there in my opinion.

DR. MARKS: How about page 26? Those are all okay?

DR. HILL: Yeah.

DR. MARKS: Okay. And everything on 27 you would delete?

DR. HILL: Yep. Because they're no longer mono ethanolamine. You've got -- now we're at tertiary amines. Singling out the mono ethanolamine moiety in those doesn't make any good sense from a biological perspective.

DR. SHANK: They're not all tertiary amines.

DR. HILL: No, okay.

DR. SHANK: Yes, the second and third one are not. I think it just was because what was to the left was so structurally dissimilar from all these other --

DR. HILL: Let's go back to Ron Shank and Tom. Do you -- using the tertiary amines as a dividing point, do you like that idea? Just eliminate tertiary amines when we look at these?

DR. SHANK: Well, they're certainly different.

DR. MARKS: Okay. So let's go -- you said, Ron Shank, so the hexyl -- what is that? Hexyloxodecanamide. That's the number two compound there. That one's okay to include? Would you include that Ron?

DR. HILL: See, I wouldn't because those are beta -- it's an amide of a beta keto acid -- branch beta keto acid. I don't know how one should think about those but they're nothing like the rest of them. And I would suggest biochemically without having any data on anything that looks like that to read-across, which I think is where we're at. No reason to believe that those would necessarily be handled the same way as the others which would undergo a mega hydroxylation, rounds of beta oxidation, chopping down to something. These would result in something very dissimilar. I'm not sure what without any information but --

DR. SHANK: Yeah, based on beta oxidation of those compounds these don't fit the rest.

DR. HILL: I'm not sure what you'd be left with without having some metabolism data but --

DR. MARKS: Okay. So everything on page 27 is eliminated. How about 28?

DR. HILL: So on 28, the only one I took out was myristol -- let's see. Similar structure. It's about halfway down. It's myristoyl/palmitoyl/oxostearmide/arachamide MEA.

DR. MARKS: Yep, okay. Ron Shank, eliminate that. Okay. And that's, again, because it's structurally dissimilar in the way it'd be metabolized is your concern. It doesn't -- I agree, it doesn't look like anything similar to the other ones. Okay. So that one. Any others?

DR. HILL: Yes. I wasn't sure quite how to think about the pantothenamide MEA. I wasn't sure that we'd be able to do read-across with the other MEA amides.

DR. MARKS: Pantothenamide. So that's the second one from the top?

DR. HILL: That's the second one from the top.

DR. MARKS: On page 29.

DR. HILL: On that one I feel a little less strongly about taking it out but I'm not sure why -- on what basis we'd leave it in either.

MS. FIUME: Dr. Hill.

DR. HILL: Mm-hmm.

MS. FIUME: Just, is the fact that there is a (inaudible) acid, does that play a role in the decision?

DR. HILL: Not without knowing whether that's even relevant..

MS. FIUME: Okay.

DR. MARKS: So we, again, if we're going to err we want to err on the safe side. So remove that one, Ron Shank? Tom? You didn't say -- you didn't say --

DR. HILL: To me it's not a no-brainier. If we want to go back to what the rule is supposed to be but we've passed that point.

DR. MARKS: Yeah, well, if it's a no-brainer it's easy. We get rid of it. Okay. Because that's exactly right. If there's any question at all we remove it.

DR. HILL: All right. The other one on this -- there are two more on this page I wasn't sure how to think about either. One, two, three, four, five, six. The sixth one down, which has got the MEA moiety as stearified with stearic acid on the opposite end.

DR. MARKS: So is that the stearamide MEAs?

DR. HILL: Stearamide MEA stearate. If we had direct toxicology data on that of some sort, any sort, I'd be all right with that, but I'm pretty confident we do not.

DR. MARKS: Okay. And then you mentioned one more.

DR. HILL: And the one right below it. Yeah, the one right below it is not a MEA amide at all.

DR. MARKS: Okay.

DR. HILL: And I took out the whole next page because they are also not MEA amides. Those are all -- I think the use of these is all different as well. These are probably low concentration emulsifying surfactants only would be my guess. But again, the rationale is there. They're not MEA amides.

DR. MARKS: Okay. So that's whittled it down dramatically. Tom and Ron, you're, okay, again with that last page. We'll make those no-brainers. So the ingredients, I need to go to page -- what's that -- 26 through 30. Just to be, Ron, to make sure I heard what you said, basically everything on page 27 is eliminated. One ingredient on 28, the myristoyl (inaudible), et cetera; 3 on page 29; and then the entire page 30.

DR. HILL: Yeah, because then we're left with a list. And I think we have things that we can use for read- across in a biochemically reasonable and toxicologically reasonable fashion.

DR. MARKS: Okay. Ron and Tom.

DR. SHANK: That's fine with me.

DR. MARKS: Okay. And then in terms of do we -- since this is simple add-on no-brainers, when we reopen this can we just read-across and the data we have, do we need any more data to reach a conclusion that's safe or safe with limitations?

DR. SLAGA: Safe when non-irritating.

DR. MARKS: Mm-hmm.

DR. SHANK: Well, I would put some concentration limits based on (inaudible) sensitization. Pardon me. So they're all safe as used except stearamide MEA, which is safe up to 5.27 percent because that's what was tested. What's used in deodorant is 15 percent.

DR. MARKS: Anything else?

DR. SHANK: That's it.

DR. MARKS: So the stearamide MEA safe up to 5 percent. Non-irritating. Formulated to be non-irritating. Formulate non-irritating.

DR. HILL: Now, I need to raise an issue but we don't have any reproductive toxicology on any of these.

DR. MARKS: Can you use --

DR. HILL: And we don't have biotransformation -- I mean, if we had even biotransformation data that suggested what happens to these is the amides are cleaved and we get fatty acid and we have plenty of data for those but I don't see that we have that data and I'm not sure that I think that that's what would happen anyway.

DR. MARKS: Can you use from the original report --

DR. HILL: That's what I was looking for.

DR. MARKS: Page 49 of the Panel Book?

DR. HILL: So what's written up out here is the teratogenicity. It seems to be just dealing with the MEA itself.

DR. MARKS: There's no data. That would be an insufficient.

DR. HILL: There sure are a mess of uses.

MS. FIUME: Dr. Marks, I don't know if it's useful at all or not but in the DEA amide report, the diethanolamides, the reproduction data were also missing. And in that one there wasn't the same paragraph with discussion that's in this discussion referencing -- it's Panel Book page 25 if you accepted it there. I don't know that it will apply here to just the amides as well but right in the middle of the page about the lack of reproductive and developmental toxicity, that paragraph is accepted in the DEA amide discussion.

DR. HILL: For me that resulted in nothing. I mean, if you had something to hang your hat on in terms of what might happen metabolism-wise that would be one thing. I'm not sure how that on the DEA amides report how that slipped past me, quite frankly. Because if that's what it says in the other report I'm not so comfortable there either.

DR. MARKS: So Ron Hill, you would prefer that this would go out as an insufficient conclusion and that we don't have the reproductive and developmental toxicity?

DR. HILL: Are we making a motion tomorrow?

DR. MARKS: No, the other team is making the motion but that doesn't change what we've concluded. So the question is do we go with this formulate nonirritating, the stearamide MEA at 5 percent limit? And then, of course, that was with a safe conclusion. Otherwise, it would be insufficient and we need reproductive and developmental toxicity to move forward with safe. And I don't -- it sounds like it's going to be difficult since this paragraph that Monice referred to talks about ethanolamine and then with amidases and skin these amides would be converted to ethanolamine and therefore that would address the issue.

MS. FIUME: I think that came from Curt, my recollection.

DR. HILL: So I don't know. Yeah, I mean, I don't know why that escape clause would have been used for the others because amidases probably don't even cleave those diethanolamine amides. I mean, all the evidence was that whatever biotransformation occurs happens at the other end of all those molecules or its conjugation, which is probably what happens here, probably removed by -- whatever penetrates probably gets removed by glucuronidation and biliary renal excretion depending on the lucidity and the size. It sure would be nice to have information to that effect.

And I don't know. We researched this a little bit. I don't remember what we concluded about amidases and the skin. Mostly in humans they're in litter and not much of anywhere else but I think there are some in skin. I just don't remember if we had any SAR data to tell us what might likely happen here.

MS. FIUME: I think this is something we've done a search on in the published literature --

DR. HILL: You couldn't find anything pertinent. That's what I thought I remember. This isn't the first time I've asked about this I'm pretty sure.

DR. MARKS: So Ron --

DR. HILL: I kicked the can down the road.

DR. MARKS: Yeah. Ron Shank, do you have a way you would lean? Do you want me to just bring it up tomorrow as an issue?

DR. SHANK: (inaudible) aren't likely to metabolize this, then we need reproductive toxicity data.

DR. MARKS: Well, why don't I tomorrow, depending -- well, it doesn't depend on what the other team -- they'll make the motion and then I'll just respond to it. If it's safe, I can bring up the issue we have. We were struggling with. We discuss insufficient versus safe as a conclusion and we had difficulty dealing with a lack of reproductive toxicity data and then see how the discussion takes us. Does that sound like a reasonable way to move forward?

DR. HILL: Yeah. You can bring up the amidase, too.

DR. MARKS: Yeah.

DR. SLAGA: I just vaguely remember --

DR. MARKS: Skin amidases.

DR. HILL: Yeah, and I brought a paper with me but I need to reread it.

DR. MARKS: And let me see. That paragraph that you so cleverly put together was -- that was on page 25 where you talked about the --

MS. FIUME: The lack of reproduction data?

DR. MARKS: Yes.

MS. FIUME: Yeah. It's pretty much right in the middle of the page.

DR. MARKS: Yeah, right in the middle. And then you mention also the amidase is in there. So, yeah. It's on the second, so that's page 25. So we're -- so basically ingredients are the first issue that we're going to -- we're going to reduce the number of ingredients. And then once we get to that point then the question is the issue of this tentative amended safety insufficient because of reproductive toxicity data versus moving forward with safe, formulated as nonirritating, and with a limit on the stearamide MEA at 5 percent.

Okay. Anything with (inaudible)?

MS. EISENMANN: (inaudible) insufficient data announcement first? I don't know (inaudible) review it's --

DR. MARKS: Well, no. Oh, yeah, it won't go to safe if we can't get over the hurdle.

MS. EISENMANN: I mean, does it go directly to tentative insufficient or do you --

MS. FIUME: I was going to check with Alan how it goes since it's a re-review.

MS. EISENMANN: I know. I would think it would go to an insufficient data announcement though.

DR. MARKS: Oh.

MS. EISENMANN: That reports directly to the tenant.

MS. FIUME: Probably but I didn't see anything since I needed to run it.

DR. HILL: Well, because, I mean, most of these are add-ons. Right? All but three.

DR. MARKS: Correct. Although doesn't this reproductive toxicity data apply for those original three?

DR. HILL: Yes.

DR. MARKS: We can, in terms of procedurally, we can, in terms of procedurally we can let Alan make that decision tomorrow. Sometimes he likes to move forward just putting out the report. We did that the last time with the use concentration that we moved forward rather than tabling it.

Okay. So we have that conundrum which we will resolve tomorrow. Okay.

DR. HILL: And it occurred to me, Monice, that the search might need to be done using lipases instead of amidases because it could be -- what could do that cleavage would be light pages that could handle amides and substrates, albeit with a substantially rate. But I'm not sure.

Ethanolamides – Full Panel – Dec 13, 2011

Moving on to the next ingredient, Dr. Belsito, ethanolamides.

DR. BELSITO: Okay. So, this is the second part of what we did back in September when we started splitting all the ethanolamides apart, and we decided on a specific family of ethanolamides to be included in this report. And this is what we're looking at.

And basically, we felt that this group could be safe as used in the present practices of cosmetics. We did have one question on the addition of sodium MEA-3 cocoamide sulfate, and it appeared in this document and not the last. But I believe, Dan, you felt that that was reasonable in this family.

DR. LIEBLER: Correct.

DR. BERGFELD: So, that's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Second?

DR. MARKS: Before seconding, I would like to --

DR. BERGFELD: Sure.

DR. MARKS: -- have a discussion.

DR. BERGFELD: Sure.

DR. MARKS: So, our team had some little different conclusions or take. First, the ingredients that would be included in this report, we felt should be changed because there -- on Panel Book, page -- and I'll go through them. Let's start with Panel Book, page 26. All the ingredients in the first page of the table would be included on that page.

Then on page 27, so the next page of that table, we felt that all those ingredients should be deleted. They were tertiary in meanings. And in the second and third compound, beta oxidation occurs, and we just didn't feel comfortable including those in this report.

We go on to -- and then I'll open it up for discussion, let the two Rons comment also. On Panel Book, page 28, the one, two, three, four, five, six, seventh -- the miristol compound would be deleted. On page 29, the second compound down, the pantothenamide MEA would be deleted. And then, if we continue, stearamide MEA stearate, and then --

DR. BELSITO: Wait a minute. Didn't we already do stearamide MEA?

DR. MARKS: Delete it out of this. These are not MEA amides.

DR. HILL: It's a stearate ester of stearamide MEA. It's not -- stearamide MEA stearate, which is the one, two, three, four, five, sixth down --

DR. BELSITO: I understand.

DR. HILL: That hasn't been --

DR. BELSITO: Correct me if I'm wrong. This document was opened after -- for a review of isostearamide, mirostamide, and stearamide MEA. What --

DR. HILL: But that's not stearamide MEA. It's stearamide MEA stearate.

DR. BELSITO: Okay.

DR. MARKS: Yeah, and you're right, Don. It is a reopen, so it should be no brainers, if I understand everything.

DR. BELSITO: Okay. So, I thought you were saying stearamide MEA.

DR. MARKS: No, I said stearate.

DR. BELSITO: Okay.

DR. MARKS: It's the middle one.

DR. BELSITO: Yeah, I see it.

DR. MARKS: And then, if we go on to the last page, page 30 of the Panel Book, all those ingredients would be deleted because they are not MEA amides. So, we could go back and go over those individually if you want with Ron and Ron commenting. But we felt these ingredients didn't belong in this report as --

DR. BELSITO: Well, Dan, what do you think?

DR. LIEBLER: So, let's just take these a group at a time if we could. I just want to make sure I follow your logic before I respond.

So, starting on report, page 11, Panel Book 27, that group -- that's everything on that page you want out, right?

DR. MARKS: Correct.

DR. LIEBLER: Okay. And the reasoning is what?

DR. MARKS: I'll let Ron Hill comment, and Ron Shank, if they want to.

DR. HILL: They're not MEA amides, and we have tertiary means where -- or tertiary amides as opposed to secondary amides.

So, the first one is -- fits that description. The second one doesn't. The second one and the third one, and then there's another one on the next page, we have suddenly a beta-keto group with an akyl chain in the middle. And we don't have any direct data on any compounds with that substructure, which means when we read across, it's going to be very problematic. That will be totally uncomfortable with read across because, presuming bio transformation occurs by some chain shortening mechanisms, we're going to end up with products that are different than in the others, or maybe not. We don't have any hard data on metabolism at all for that group of compounds, any of those.

And so, for me, I can't read across. They definitely don't fall in the no-brainer category.

DR. LIEBLER: All right. And then, so duly noted. Then the next -- so do you have an issue with tertiary amides in this context, because you've got -- you mentioned the beto- keto, the branch chain beta-keto substituent, which will be

the hexyl oxodecenomide MEA and the phosphate below it. And then, you also mentioned the tertiary amides. So, there's an issue with those --

DR. HILL: Yes.

DR. LIEBLER: -- in your mind?

DR. HILL: Yes. Okay. And then on that same page actually, the one, two, three, fourth one down, it's not an MEA amide because we have a hydroxy ethyl group tacked onto the alcoholic moiety of MEA, and that makes it a completely different compound.

DR. LIEBLER: Well, it still is an MEA amide because it's got an MEA off the other -- the other substituent on the nitrogen is an MEA, right?

DR. HILL: Well, yes.

DR. LIEBLER: I mean, it's -- you know, it's essentially two carbons ending with a hydroxyl. I actually -- obviously, you know, historically we've had a somewhat different set point on no-brainers, Ron, so I'm just trying to bridge the gap here. But I actually don't share your concern about those compounds, particularly the tertiary amides.

DR. HILL: Well, we haven't got to the reproductive toxicology issue, so maybe if we could wrap back around considering that particular one.

DR. LIEBLER: Well, why don't we delete that then?

DR. HILL: Okay. But my point is with the fourth down is, it's no longer an MEA amide because there's a hydroxy ethyl moiety, so the oxygen is no longer -- it's no longer a monoethanolamine. We now have monoethanolamine ether.

DR. LIEBLER: So, there's a -- I think there's a broader point for some of these, which is that if the MEA amide, the hydroxyl on that, has been esterification with another longer chain substituent, those are in your team's not no-brainers anymore.

DR. HILL: In this case it's ether rather than an ester, so, yeah. Yes.

DR. LIEBLER: Well, yeah, but in another case, the one that Don raised, it was an esterification of that hydroxyl, right?

In any case, I take the point. So, I guess I would be okay with deleting those, which would be stearic mitoethylethanolamine -- I'm sorry, the stearamide MEA stearate, which is on Panel Book 29.

DR. HILL: Yes.

DR. BELSITO: And the pantothenamide MEA was the other on 29 they were requesting be dropped.

DR. HILL: And actually, we sort of discussed that is, does this really fit or not? It certainly an MEA amide. We're talking about the second down --

DR. LIEBLER: Right.

DR. HILL: -- on page 29. What's at the other end is quite different, and there's this amino propyl linker in between with another amide, so that makes it really, I think, drastically different. But if we have direct data on that compound, then it, you know, could stay in. But if we don't have any toxicology whatsoever on it, then -- didn't we determine there aren't any current uses of that one that were reported?

DR. LIEBLER: Well, that should be beside the point.

DR. HILL: It is beside the point.

DR. LIEBLER: Yeah.

DR. HILL: But, I guess, I'm saying the consequences for removing it, not that great.

DR. LIEBLER: So, I guess what we have presented to us here is kind of a grab bag of structures grafted onto ethanolamide, right? I mean, is that a fair way to put it, guys? And the question is, how comfortable or how much these are no-brainers with respect to safety evaluation, not necessarily whether we have hunches about what's good or bad.

DR. HILL: No, it pertains to the ability to read across the tox data is what I'm saying.

DR. MARKS: And, Dan, don't forget on page 30, all those we suggested --

DR. LIEBLER: Yeah, right.

DR. MARKS: -- be removed.

DR. HILL: To me, the ones on page 30 represent their own class.

DR. LIEBLER: I would agree with that.

DR. BERGFELD: Do I hear you, Dan, agreeing with what has been proposed by the Marks' group?

DR. LIEBLER: With a lot of it. The last page, yeah, I do agree. I also agree with the deletion of the ones in which the hydroxyl substituent of the ethanolamide has been modified either as esterified or converted to an ether. Ron?

DR. BELSITO: So, which ones would those be, Dan?

DR. LIEBLER: Let's see.

DR. BELSITO: We're getting all --

DR. LIEBLER: Stearamide MEA stearate.

DR. BELSITO: Okay. What about pantothenamide MEA?

DR. LIEBLER: I don't have a problem with that. I think that can stay.

DR. BELSITO: Okay.

DR. HILL: But there's a hydroxy ethyl pantothenamide MEA where that oxygen is modified, and it's no longer an MEA amide. That's the fourth one down on page 27.

DR. BELSITO: Let's take it one at a time.

DR. HILL: Okay.

DR. BELSITO: Okay? Then moving --

DR. HILL: Well, I want to make sure you're --

DR. BELSITO: Moving to page 12 then, do you agree that miristol oxo stearamide or erucamide MEA should be removed, which was the one -- only one on page 12 that you wanted removed, correct?

DR. MARKS: That's correct.

DR. LIEBLER: And this is because of this beta-diketo functionality, Ron?

DR. HILL: Yes, that structurally it is very different from the ones that we actually have safety data for.

DR. LIEBLER: Well, it's different, yeah. I guess I didn't have an alarm about it, but I guess if you have a concern, then it's not a no-brainer.

DR. BELSITO: Okay. So, you're fine with that. And then, Dan, page 27, every single one on page 27 was suggested to be deleted.

DR. LIEBLER: I suppose these could comprise their own family, many of them, but the two -- the second two on page 27 are distinct and unique, again, as beta-diketos. If you're concerned about that, we'll go -- those can go. I guess the others could be put together at some other point.

DR. BELSITO: So, you're okay with all of the deletions?

DR. LIEBLER: I'm okay with the deletions.

DR. BELSITO: So, the point of contention is the pantothenamide MEA.

DR. HILL: And I didn't flag that for definite deletion. When we talked about it yesterday, I wanted to see what the other group -- this was a case where I wanted to see what the other group. Just we'll have to have a lot more reflection between now and the next time. You know, do we have enough data to actually read across here? So, I mean, leaving it in's okay with me right now.

DR. BELSITO: It would be nice to go final since we looked at the grouping at the last meeting, and we agreed to this grouping. And now suddenly we're not agreeing to the groupings, so...

DR. HILL: I don't remember agreeing with this grouping, so I'm not sure when that happened or how. But I can't --

DR. MARKS: I think what we did was just split it out.

DR. HILL: We split it out, and then we said we'd come back and look at these is my recollection of what we actually did. So, that's not what the minutes said, but that's my recollection of what we actually did.

DR. LIEBLER: So, with that pantothenamide, if you break that down to substructures, Ron, I don't see anything that is -- that was raised about the other compounds that caused concerns. That's why I don't think that one needs to be deleted.

DR. HILL: No. It's just I'm not sure we have any supportive data in terms of read across. That's what bothered me, because it looks dissimilar. And when we talk about the next thing we're about to talk about, I'll explain my logic.

DR. BERGFELD: So, you're leaving that one in?

DR. LIEBLER: I think that should be left in.

DR. HILL: Because we're going to have to talk about the activity of palmitoyl MEA and its role in the endocannabinoid system, and the fact that it has biological activity, and that we don't have any reproductive toxicology, which is the rest of our discussion yesterday. On any of these do we have repo tox.

MR. ANDERSON: And just to clarify procedurally, at the last meeting, one, you did agree on what the vast scope of the family would look like. Having second thoughts is okay, but we did do that at the last meeting.

But what you instructed us to do was to prepare a draft of a tentative report. If you agree with whatever scope in hindsight, whatever, this is going to go out for public comment. This doesn't go final. This is to go out as a tentative.

DR. BERGFELD: So, I'd like to know where we are on Panel Book, page 29. You have left the second ingredient in, is that correct?

DR. LIEBLER: Correct.

DR. BERGFELD: And then the -- there is a stearate --

DR. BELSITO: You're okay with that, Ron Hill?

DR. BERGFELD: Yes, he is.

DR. HILL: Yes, sir. Yes. Yes.

DR. BERGFELD: And the stearate, which is the one, two, three, four, five, six --

DR. BELSITO: Stearide MEA stearate is out.

DR. BERGFELD: Is out. Is that the -- that's the only one on that page is out.

DR. MARKS: Correct.

DR. BELSITO: So, we've agreed with all the deletions except pantothenamide MEA, which they've agreed to put back in.

DR. MARKS: Correct.

DR. BERGFELD: All right. Can we get clarification on the one that's under the stearamide MEA stearate, which is the --

DR. MARKS: Out.

DR. BERGFELD: How?

DR. BELSITO: Steaamido ethyl.

DR. BERGFELD: Yeah.

DR. MARKS: That's -- as I went through with Ron Hill --

DR. BERGFELD: Is that out?

DR. MARKS: -- that we felt that should -- that's not an MEA amide.

DR. BELSITO: Well, I didn't hear you say that before. So, stearo mito --

DR. LIEBLER: Yeah, it's not. That's actually a secondary amine.

DR. BELSITO: So, you're okay with that going out?

DR. LIEBLER: Yeah.

DR. BELSITO: Okay.

DR. BERGFELD: Okay. Any other clarifications? No? Okay. So, with those changes, may we have a second?

DR. MARKS: No. I think there still needs to be --

DR. BERGFELD: Okay.

DR. MARKS: -- more discussion.

DR. BERGFELD: All right. Please, go ahead.

DR. MARKS: When we came to the decision point of safe formulated to being non-irritating and put a limit on stearamide MEA five percent. But then the issue of reproductive toxicity came up, and a lack of data to support its safety with reproductive toxicity.

So, we were really torn with that, and either going out with a safe as a conclusion, or an insufficient. And, Ron Hill, if you want to comment more, or Ron Shank, but I think I've summarized where we were. We spent some time looking across all these to see if we could get any reproductive toxicity data that would support the safety, and we came up empty handed. So, I would say we probably lean toward a tentative amended assessment with a conclusion of insufficient. Is that captured correctly, Ron, and Ron, and Tom?

DR. BERGFELD: Ron Shank, do you want to comment?

DR. SHANK: Well, in our discussion -- this is Dr. Hill's concern. But the lack of productive and developmental toxicity, we said would not be a concern because amadases would hydrolyze these. And Dr. Hill was concerned that that may not be the case. We have reproductive toxicity data for ethanolamine, but not for the amides. Is that correct?

DR. BERGFELD: Curt, do you care to comment?

DR. KLAASSEN: That's what I was looking at. We do have toxicity on the ethanolamine, and I guess I thought that would be sufficient. But I'm willing to listen to others.

DR. BERGFELD: Okay.

DR. LIEBLER: So, is the concern that the ethanolamide -- intact ethanolamides would have reproductive toxicity as opposed to the possible cleavage products?

DR. HILL: Yes. Palmitoyl MEA is a known ligand for PPAR-alpha. There is known biological activity where it augments the activity of an anandamide, which is an endogenous cannabinoid. Anandamide is arachidonoyl MEA. There are specific transporter systems for arachidonoyl MEA, which is anandamide, and there are some recent references -- actually they started in 2001, but the information has gotten more vigorous. We had this review article in 2009 that discussed some of these, and it gives some cross references, and there are some -- I think there's some forward references.

So, I think the main issue is that we -- we're making a statement amidases would hydrolyze this in skin. And we didn't come up with anything on the literature search, but it's clear to me looking at this again last night that there is -- there are fatty acid amide hydrolases that are specifically expressed in keratinocytes, sebocytes, some of the hair follicle cells. But they're expressed, of course, in a certain -- to a certain degree, and I would think with high concentrations.

If we got a significant amount in the skin, it's unclear whether they would be fully hydrolyzed so that the only thing systemically bioavailable would be only the fatty acids in monoethanolamine. If we had information about that, which we do not, then we could rely on the toxicology that comes from the fatty acids themselves. But we don't have any information either way. Are they hydrolyzed completely in the skin to the extent that some of them would penetrate into the skin? Are they doing something very significant in the skin, because this talks about effects on self-proliferation, either down regulation and triggering apoptosis, or stimulating, in some cases, proliferation. But, again, there's a reinforcement by -- specifically palmitoyl MEA, but we don't have -- we haven't captured any of the structure activity information as opposed to, you know, if we change that fatty acid structure, what will it do to that activity.

So, I think we need to capture that. And, in my mind, we can start with the insufficient data with reprotox, because if these things are bioavailable and they're modulating nuclear receptors, like PPAR-alpha, and we have to know what the potential consequences of that might be. We have known biological activity for at least one of these compounds in modulating epitotic pathways, and their mechanisms, and through action on the cannabinoid system.

At least one of these is a known vanilloid receptor, specifically TpPR-1 ligand, so their mechanism for that as well.

DR. LIEBLER: So, I think, Ron, you're invoking a lot of potential mechanisms.

DR. HILL: No, I'm invoking known mechanisms, not potential mechanisms. I mean, we know about one compound. We don't have the SAR, so --

DR. LIEBLER: Potential interactions with a series of receptors, you've mentioned --

DR. HILL: Yes.

DR. LIEBLER: -- vanilloid, transporters for --

DR. HILL: Anandamide.

DR. LIEBLER: -- compound related to anandamide, right. So, you know, I suppose the problem with many of these hypotheses is that we do know that many of these receptors show really significant specificity for, you know, for fatty acyl chain length, saturation, unsaturation, and so forth. So, you know, for example, you mentioned the palmitoyl -- palmitimide MEA. You know, sure, it's a fatty acid derivative of MEA. Sure, it has a very superficial similarity to arachidonoyl -- sorry, arachidonic acid MEA derivative. But I'm not sure that I'm comfortable making leap mechanistically to saying that this is going to modulate with a significant offendi one of these receptor systems.

DR. HILL: There's a reference on the activity at PPAR-alpha. We have a hard reference on that, and it's -- and, grant you, it's strictly the palmitoyl. I don't know the SAR on that. I don't know if the SAR has even been characterized.

But the point is, there's an unknown, and if you're modulating nuclear receptors, and you have zero data on any of them for reprotox, to me that's a big problem.

DR. KLAASSEN: But we -- you know, you're assuming that a PPAR-alpha agonist is going to be a teratogen.

DR. HILL: No, I'm saying if it's known to modulate apoptotic pathways, there could be some developmental effects. And, yes, there's the potential for teratogenicity, if it hasn't been proven otherwise.

I guess, you know, with zero reprotox data on any of these, I'm uncomfortable.

DR. KLAASSEN: Yeah. We've got MEA, and, okay. I guess, you know, going through the PPAR-alpha pathway, I mean, we've had drugs on the market for 50 years that are PPAR agonists, namely clofibrate. And it's not a teratogen.

DR. HILL: It's not?

DR. KLAASSEN: No.

DR. HILL: I think there's some question marks about that actually as of recently.

DR. SNYDER: I mean, I looked at the total set. We've been very, very high LD50s in these compounds. And if you looked at PPAR-alpha agonists, do we have any data on what their LD50s are in regards to if that pathway is invoked in the worst case scenario? I mean, we have very high LD50s, gram quantities, and both dermal and oral, and I would expect if that was a pathway, that we would see lower LD50s.

DR. HILL: If we have data showing that it doesn't get systemic, then we'd only be concerned with any potential effects in the skin. And, you know, actually they may be all beneficial effects, and it would be nice to have some SAR on that, which, in most cases, we still don't. I mean, effects on keratinocyte populations, for example, we don't have data reflecting that, best I can tell. So, again, are there any effects on dermal tumor growth rates? We don't have any information on that, so back up from the reprotox.

I'm just bothered because we don't have enough SAR to know what is the potential for some of these relatively artificial compounds to have the same kinds of effects. Just me, but...

DR. LIEBLER: So, the core of your concern is the lack of repro developmental toxicity for this family of compounds. Basically that's the core issue?

DR. HILL: That's really the most serious issue, in my mind.

DR. LIEBLER: Okay. Another way of putting it then.

DR. BELSITO: And the relative concentrations of use, around five percent at the highest and in dermal leave- on? Those are the satisfying.

DR. HILL: Well, you know, again, if we're -- the problem, in my mind, is we're relying on hypothetical amidases and skin hydrolysis rate, which has not been characterized. So, if we know none of these compounds are leaving the skin because they get into the skin slowly, and those amidases are, in fact, there and they are, in fact, doing completely cleavage, and the only thing that enters the system is fatty acids and MEA, then that changes the toxicology. But we don't have that information. If we did, we'd be good, in my mind, because, you know, the amounts are modest. Dermal penetration for some of these would be very low. Probably penetration into the system might be zero or practically zero, and we'd be good. But we don't have information that either.

So, one way or another, to me, it seems like you have to have -- if you're going to say "safe," you have to have some information, some science on which to rest that.

DR. BERGFELD: I think now we're talking in circles, a little bit in circles right now. And so, we have a motion that's been made. It's not been seconded. Are there any new points to be made as discussant points?

DR. LIEBLER: I'd just like to underscore that I think I'm more comfortable with the totality of the data set, very large dermal LD50s. I don't think it's very likely that these compounds would be quantitatively cleaved by amidases. So, if there is some absorption, some small amount of these compounds could be systematically bioavailable, but the amounts would be very small.

And I think that gets to the issue of any potential mechanisms involving, you know, receptor interactions with a very small amount of agonists that are not really optimal for stimulating these systems, I think that my level of concern about that is just -- is significantly lower than what I've heard from you, Ron. That's all.

DR. BELSITO: So, could I make a new motion --

DR. BERGFELD: Yes.

DR. BELSITO: -- that we will agree with all of the deletions that were initially proposed by the Marks' team, with the exception of pantothenamide MEA, which we'll keep in the report, and that we go as "safe as used," with the usual nitroso boiler plate and the inhalation boiler plate, if that's relevant to this document. And I'd like to make that move, and see what the vote shows.

DR. BERGFELD: May I ask -- are you seconding it, Paul?

DR. SNYDER: Second.

DR. BERGFELD: May I ask a question? Would you include in your discussion any of the issues that are on the table now?

DR. BELSITO: Of course. Of course.

DR. BERGFELD: Okay.

DR. BELSITO: The discussion would be cleavage, the concentration of use, the low amount of the receptors. I mean, I think we need to bring all of these points into the discussion. But I think what we're hearing is some people have issues, some people don't have issues. Let's vote and see where the dye is cast.

DR. MARKS: I'd like to clarify that. Do you want to formulate it so these ingredients are non-irritating?

DR. BELSITO: Of course, yes.

DR. MARKS: Okay. And then, we thought that we might set a limit on stearamide MEA at five percent.

DR. BELSITO: That was set for irritation. I think we take care of that by formulating it not to be irritating.

DR. MARKS: Say non-irritating. Okay. And then, Dan, if I hear you correctly, you would re-craft that paragraph on page 25 in the discussion, the one where it says, "The specific concern of the panel was lack of reproductive and development toxicity," and just embellish that with, what I heard, the main thing you said was there would be so little available systemically that we would not be concerned that the amidases are the real reason that there's a lack of concern.

DR. LIEBLER: Correct.

DR. MARKS: Okay.

DR. BERGFELD: All right. Any other points that need to be made? Tom? Ron? Ron Hill, closing remarks? You okay? All right.

Call for the question. All those in favor of the proposed safe with the caveats that have been added? All right. Opposed? Opposed. One opposing? And the remainder, which is eight.

Okay. So, we'll move on then. Thank you for that discussion. It will be all recorded in the minutes.

Report

Draft Final Amended Safety Assessment

Ethanolamides as Used in Cosmetics

March 5, 2012

The 2012 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 Director is F. Alan Andersen, Ph.D. This report was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer and Bart A. Heldreth, Ph.D., Chemist.

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ABSTRACT

The CIR Expert Panel re-reviewed the safety of isostearamide, myristamide, and stearamide MEA as used in cosmetics, and included 25 additional ethanolamides that are secondary carboxamides comprised of the amidation products of alkyl carboxylic acids and ethanolamine. Most of the ethanolamides are reported to function in cosmetics as hair conditioning agents, skin conditioning agents, and surfactant – foam boosters; a few are reported to have other uses. The Panel reviewed available animal and clinical data, as well as information from previous CIR reports. The Panel concluded that these ingredients are safe in the present practices of use and concentration when formulated to be non-irritating, and that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

INTRODUCTION

The CIR Expert Panel re-opened the safety assessment of isostearamide MEA, myristamide MEA, and stearamide MEA. These ethanolamides were reviewed in 1995.[1] In that previous safety assessment, the Panel concluded that these three ingredients were safe for use in rinse-off products. In leave-on products, these ingredients were safe for use at concentrations that will limit the release of free ethanolamine to 5%, but with a maximum use concentration of 17% for isostearamide, myristamide, and stearamide MEA. At that time, concentration of use data were not available and the Panel relied on test data to establish limits for use concentrations. The report conclusion went on to state that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

The following additional 25 ingredients are being included in the re-review of isostearamide MEA, myristamide MEA, and stearamide MEA. The ingredients within the ethanolamides group are secondary carboxamides comprised of the amidation products of alkyl carboxylic acids and ethanolamine.

Acetamide MEA
Azelamide MEA
Babassuamide MEA
Behenamide MEA
C16-22 Acid Amide MEA
Cocamide MEA
Cocamide Methyl MEA
Cocamidopropyl Betainamide MEA Chloride
Hydroxystearamide MEA
Lactamide MEA
Lauramide MEA
Linoleamide MEA
Oatamide MEA
Oleamide MEA
Oliveamide MEA
Palm Kernelamide MEA
Palmamide MEA
Palmitamide MEA
Pantothenamide MEA
Peanutamide MEA
Ricinoleamide MEA
Sunfloweramide MEA
Tallowamide MEA
Trideceth-2 Carboxamide MEA
Undecylenamide MEA

In addition to the earlier safety assessment of isostearamide MEA, myristamide MEA, and stearamide MEA noted above, certain ingredients on this list also have been reviewed previously by the CIR Expert Panel. In 1993, the Panel concluded that acetamide MEA is safe as used as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products, based on sensitization test data, and is safe in the present practices of use in rinse-off products; cosmetic formulations containing acetamide MEA should not contain nitrosating agents or significant amounts of free acetamide.[2] Data from 1989 reported acetamide MEA was used at up to 25% in rinse-off products. This conclusion was reaffirmed in 2008. Cocamide MEA was reviewed in 1999; the Panel concluded that cocamide MEA is safe as used in rinse-off cosmetic products and safe at concentrations up to 10% in leave-on products.[3] Cocamide MEA was reported to be used at up to 25% in 1984, but the types of products, i.e., rinse-off or leave-in, were not specified. The Panel also noted that Cocamide MEA should not be used as an ingredient in cosmetic products containing *N*-nitrosating agents, or in product formulations intended to be aerosolized. The leave-on concentration limit was derived from the concentration found safe at the time for cocamide DEA; the inhalation caveat was based on concerns of inhalation toxicity of ethanolamine.

The structures and definitions of the ethanolamides are provided in Table 1. The conclusions of the previously reviewed ingredients, as well as of relevant acids that have been previously reviewed by CIR, are provided in Table 2.

Information relevant to the safety of ethanolamides was included in the previous reports noted above. Information from those reports has been given below in single spaced, indented text in the relevant sections.

CHEMISTRY

The ethanolamides consist of covalent, secondary amides, whereby one of the nitrogen substituents is ethanol and the second is a carbonyl attached substituent. For example, myristamide MEA is a secondary amide wherein one of the nitrogen substituents is ethanol and the second is a fourteen carbon, carbonyl attached chain (Figure 1). These ingredients are not salts and do not readily dissociate in water. However, amidases, such as fatty acid amide hydrolase (FAAH) which is known to be present in human skin, could potentially convert these amides to ethanolamine and the corresponding fatty acids.[4-6] Secondary amides do tend to react with nitrosating agents to form nitrosamides.

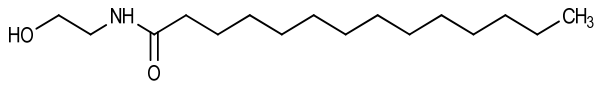


Figure 1. Myristamide MEA

Chemical and physical properties of ethanolamides are summarized in Table 3.

Method of Manufacture

Ethanolamine reacts with long-chain fatty acid esters in a 1:1 mole ratio to produce a 90+% pure, crystalline ethanolamide mixture.[7]

Two different routes of synthesis of ethanolamides are common: direct acylation with free fatty acids and transacylation using fatty acid esters (often enzymatically).[8,9] Ethanolamides can be produced via enzymatic amidification; monoacylated ethanolamine can be isolated from the reaction mixture. The reaction is carried out using an equimolar ratio of fatty acid and ethanolamine. The enzyme is filtered upon completion of the reaction, and the product is dissolved in a mixture of methanol and chloroform. The solvent is then eliminated by evaporation, and the resulting solid is the amide.

Acetamide MEA

Acetamide MEA is prepared by the reaction of acetic acid with ethanolamine. Additional methods of production, involving acetamide and ethylene oxide, ethanolamine and acetyl chloride, have been reported.

From The Final Report on the Safety Assessment of Acetamide MEA[2]

Impurities

Acetamide MEA

Analysis of 4 lots of acetamide MEA by gas chromatography-mass spectrometry indicated the presence of 0.0006-0.0029% ethanolamine and 0.0006-0.0030% acetamide. Using high-performance liquid chromatography, *N*-nitrosodiethanolamine was not detected (limit of detection = 0.05 ppm) in acetamide MEA.

From The Final Report on the Safety Assessment of Acetamide MEA[2]

Myristamide MEA

The maximum free amine content of myristamide MEA is 1.5%.

From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[1]

Stearamide MEA

Stearamide MEA has 0.8% max. free fatty acids (as stearic acid), 0.5-2.0% free amine (as ethanolamine), and 54.0-58.0% total fatty acids (as stearic acid).

From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[1]

USE

Cosmetic

Most of the ethanolamides are reported to function in cosmetics as hair conditioning agents, skin conditioning agents, and surfactant – foam boosters; a few are reported to have other uses.[10] Voluntary Cosmetic Registration Program (VCRP) data obtained from the Food and Drug Administration (FDA) in 2011 report that stearamide MEA is used in 10 cosmetic formulations, myristamide MEA is used in 1 formulation, and isostearamide MEA does not have any uses reported.[11] Other ethanolamides included in this safety assessment have many more reported uses. For example, cocamide MEA has the highest frequency of use, with 1122 reported uses; only 33 of those uses are in leave-on products. Trideceth-2 carboxamide MEA has 189 reported uses, and acetamide MEA is reported to be used in 148 formulations.

According to data submitted by industry in response to a recent survey conducted by the Personal Care Products Council (Council), cocamide MEA is reported to be used at up to 18% in rinse-off formulations and at up to 5% in leave-on formulations.[12] Stearamide MEA has the highest concentration of use in leave-on formulations at up to 15%. The use information for the ethanolamides is provided in Table 4a. In some cases, reports of uses were received by the VCRP, but no concentration of use data were available. For example, acetamide MEA is reported to be used in a nail formulation, but no use concentration was available. In other cases, no reported uses were received in the VCRP, but a use concentration was provided in the industry survey. For example, lauramide MEA was not reported in the VCRP to be used in baby product formulations, but the industry survey indicated that it was used in such products at 0.5%. It should be presumed that lauramide MEA is used in at least one baby product. Ethanolamides that are not reported to be in use, according to VCRP data and the Council survey, are listed in Table 4b.

A few of the ethanolamides may used in products applied to baby skin or used near the eye area or mucous membranes. Additionally, some of the ethanolamides are used in cosmetic sprays, with reported maximum use concentrations of 0.4% acetamide MEA in aerosol hair sprays and 1% cocamide MEA and lauramide MEA in foot sprays.[12] These products 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.[13,14] 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.[15,16] However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions may cause toxic effects depending on their chemical and other properties. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[16] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Monoalkylamines, monoalkanolamines, and their salts are listed by the European Commission in Annex III Part 1: the list of substances which cosmetic products must not contain, except subject to the restrictions and conditions laid down.[17] These ingredients are allowed a maximum secondary amine content of 0.5% in finished product; are not to be used with nitrosating agents; must have a minimum purity of 99%; the maximum secondary amine content of 0.5% is allowed for raw materials; maximum nitrosamine content allowed is 50 µg/kg; and the chemicals must be kept in nitrite-free containers. Acetamide MEA and babassuamide MEA are the only ethanolamides listed in this category. All the other ethanolamides are listed in the EU inventory.

TOXICOKINETICS

Published toxicokinetic data were not found.

TOXICOLOGICAL STUDIES

Acute (Single) Dose Toxicity

Dermal

Acetamide MEA

No deaths occurred when rabbits were dosed dermally with 20 ml/kg acetamide MEA.
From The Final Report on the Safety Assessment of Acetamide MEA[2]

Cocamide MEA

The dermal LD_{50} of cocamide MEA was evaluated by applying 2 g/kg to the abraded and intact skin of rabbit under occlusive patches. [18,19] The dermal LD_{50} in rabbits was >2 g/kg.

Oral

Cocamide MEA

The acute oral toxicity of cocamide MEA (purity not specified) was evaluated in a number of studies using rats.[18-20] In most studies, the highest dose administered was 5 g/kg or 5 ml/kg; the LD_{50} was greater than this dose. In a study in which doses of 1-32 g/kg were used, the LD_{50} was reported to be 7.4 g/kg in rats[18,19] In two other rat studies, the oral LD_{50} of cocamide MEA was identified as 3.3 g/kg and >3.125 g/kg, respectively.[20] In studies in mice, the oral LD_{50} of cocamide MEA was >10 g/kg in most studies. However, a value of 3.125 g/kg was reported in one study using mice. (Details were not provided.)

Acetamide MEA

The oral LD_{50} of acetamide MEA has been reported as 26.95 and as 27.66 g/kg in rats. The acute LD_{50} of two hair products containing 1.3% acetamide MEA was >16.9 g/kg for one product and >25 ml/kg for the other; these were the highest doses tested.
From The Final Report on the Safety Assessment of Acetamide MEA[2]

Lauramide MEA

The oral LD_{50} of lauramide MEA was >2 g/kg in rats.[21]

Repeated Dose Toxicity

Dermal

Acetamide MEA

In a 13-wk study, a hair product containing 1.3% acetamide MEA, applied as an aq. solution that was diluted to 50% w/v, was not toxic to rabbits. Slight-to-moderate erythema was observed sporadically at the application site from days 44-84 of the study.
From The Final Report on the Safety Assessment of Acetamide MEA[2]

Cocamide MEA

Cocamide MEA, 25% in olive oil, was applied to mice twice a day for 1 wk and the application site was not covered.[20] No dermal reactions were observed. Additional details were not provided.

Stearamide MEA

The dermal toxicity of a formulation containing 17.0% stearamide MEA was evaluated in a 4-wk study in rabbits. Two g/kg of a 10% aq. solution of the formulation was applied to intact and abraded skin; no gross or microscopic lesions were observed. In a 13-wk dermal study, a formulation containing 5.27% stearamide MEA was not toxic in rats.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[1]

Oral

Cocamide MEA

Groups of 10 male and 10 female Wistar rats were dosed by gavage with 0, 70, 250, or 750 mg/kg bw/day cocamide MEA in olive oil; the high dose was increased to 1500 mg/kg bw after 14 days.[18] The animals were dosed once daily, 5x/wk, for 4 wks. Recovery groups of 5 male and 5 female rats per dose level were included. None of the animals died, and no significant test-article related gross or microscopic lesions were observed. The NOAEL was >750 mg/kg bw/day.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on the reproductive and developmental toxicity of the ethanolamides were not found. Since ethanolamine may be present as an impurity in the ethanolamides, and since amidases in the skin could possibly convert some of the ethanolamide to ethanolamine and the corresponding carboxylic acid, a summary of available data from the reports on ethanolamine and the substituents of these ethanolamides is being provided.

MEA: In a dietary study, 0-7800 ppm of a composite hair dye and base containing 22% ethanolamine was fed to 60 gravid female rats on days 6-15 of gestation, and the rats were killed on day 19 of gestation. No developmental effects were observed. In another dietary study, 30 male rats were fed 0-7800 ppm of the hair dye for 8 wks prior to mating with female rats that were being fed a basal diet, while a group of 60 female rats were fed 0-7800 ppm of the test substance for 8 wks prior to mating with male rats being fed a basal diet. No effects on reproduction or fertility were observed. In rabbits, no developmental effects were observed when pregnant females were dosed by gavage on days 6-18 of gestation with 0-19.5 ml/kg/day of the hair day containing 22% ethanolamine.[22]

Arachis Hypogaea (Peanut) Oil Peanut oil was used as the vehicle in a fertility study in rats. It was administered orally for 28 days prior to mating and for 6 days during mating. No unusual findings were noted in the vehicle group. No unusual findings were observed in a teratogenicity study in which rats were injected with a test article, and peanut oil was used as the vehicle. Treatment-related changes were not observed in a study in which rabbits were dosed intramuscularly with 21% peanut oil on day 8 of gestation. However, in a study of the effects of oil vehicles on early embryonic lethality in mice, it was stated that plant oils proved to be unsuitable carriers of test mutagens in female dominant-lethal studies where the route of administration is via the peritoneal cavity.[23]

Hydroxystearic Acid The dermal teratogenicity of two formulations containing 7% hydroxystearic acid was evaluated using female rats. No teratogenic effects were observed. (However, dermal irritation was reported.)[24]

Palm Oil: Crude palm oil was not a reproductive toxicant in a study in which male and female Wistar/NIN inbred weanling rats were fed a diet containing this ingredient (10%) prior to mating. Mean litter sizes were comparable between test and control groups. No significant changes were found in liver or kidney weight in adult animals. Neither untreated palm oil (15%) nor 15% heated palm oil in the diet induced anomalies with respect to fertility and in utero growth when fed to male and female Sprague-Dawley SPF rats prior to mating. In a study investigating the effects of palm oil on sexual maturation and endocrine function, vaginal opening was observed significantly earlier (compared to 5% corn oil control) in weanling rats fed 20% palm oil in the diet. No significant differences were observed in endocrine function as determined by measuring estradiol, prolactin, and luteinizing hormone.[25]

Palm Kernel Oil: In the second generation resulting from the mating of adult Mongolian gerbils fed diet containing 8.75% w/w palm kernel oil, no statistically significant differences were found with respect to the following: frequency of litters, mean litter size, total of newborns, and suckling death. Animals receiving a basal diet served as the control group.[25]

GENOTOXICITY

In Vitro

Acetamide MEA

Acetamide MEA, ≤5000 µg/plate, was not mutagenic in the presence or absence of metabolic activation in an Ames test, and ≤5000 µg/ml acetamide MEA did not induce unscheduled DNA synthesis in primary rat hepatocytes.

From The Final Report on the Safety Assessment of Acetamide MEA[2]

Cocamide MEA

In an Ames test, 50 µg/plate cocamide MEA was mutagenic in *Salmonella typhimurium* TA100 with metabolic activation; it was not mutagenic with *S. typhimurium* TA98, TA1535, TA1537, or TA1538, with or without metabolic activation or in TA100 without metabolic activation. Cocamide MEA was not mutagenic in a plate incorporation assay.

From The Final Report on the Safety Assessment of Cocamide MEA[3]

The mutagenic potential of cocamide MEA was evaluated in an Ames test using *S. typhimurium* TA1535, TA1537, TA1538,TA98, and TA100, with and without metabolic activation.[18,19] Cocamide MEA, evaluated at doses of 4-2500 µg/plate, was not mutagenic. (No data for controls was provided.)

Lauramide MEA

The mutagenic potential of lauramide MEA was evaluated in an Ames test with *S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538 at doses of 33-3333 µg/plate, with and without metabolic activation.[26] Doses of 3.3 and 10

µg/plate were tested with TA1537 without metabolic activation, and a dose of 10 µg/plate was tested in strains TA100 without metabolic activation. Negative controls were used and gave expected results. Lauramide MEA was not mutagenic in this assay.

CARCINOGENICITY

Data on the carcinogenicity of ethanolamides were not found. Since ethanolamine may be present as an impurity in the ethanolamides, and since amidases in the skin could possibly convert some of the ethanolamide to ethanolamine and the corresponding carboxylic acid, a summary of available data from the reports on substituents of these ethanolamides is being provided.

Cocamidopropyl Betaine The carcinogenic potential of a non-oxidative hair dye formulation containing 0.09% active cocamidopropyl betaine was determined in Swiss Webster mice. A dose of 0.05 ml per mouse was applied 3 times weekly for 20 months to interscapular skin that was clipped free of hair. Dermal changes were noted, but the incidence of neoplasms in treated animals did not differ significantly from control groups.[27]

Hydroxystearic Acid In an 18-month subcutaneous carcinogenicity study in female Swiss-Webster mice, hydroxystearic acid was injected subcutaneously twice weekly for a total dose of 4 or 80 mg delivered in a total of 8 ml tricaprylin. Hydroxystearic acid was classified as tentatively carcinogenic in Swiss-Webster mice. Subcutaneous sarcomas were observed at the site of injection in 9 of the 28 mice (14 per dose group) that were alive at 6 months. All of the sarcomas were observed in the low-dose group. In a second study in which nine A/He male mice received a total intraperitoneal dose of 60 mg hydroxystearic acid over a period of 4 weeks, the frequency of lung tumors was within the spontaneous occurrence.[24]

Lactic Acid Female rabbits were dosed by gavage with 0.1-0.2 g/kg lactic acid in 100-150 ml water twice daily for 5 mos, and five female rabbits were dosed orally with 0.1-0.7 g/kg lactic acid in 50-100 ml water twice daily for 16 mos. No tumors were reported.[28]

Lauric Acid Feeding of up to 50 g/kg/day dietary stearic acid to mice was not carcinogenic. Treatment of mice with repeated subcutaneous injections of 25 and 50 mg lauric acid was not carcinogenic. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of 25 and 50 mg palmitic acid and up to 82 mg stearic acid.[29]

Oleic Acid Intestinal and gastric tumors were found in mice receiving dietary oleic acid at daily concentrations up to 200 mg/mouse. No malignant tumors were induced by repeated subcutaneous injections of 1-16.5 mg oleic acid in two species of mice. [29]

Palmitic Acid Feeding of 50 g/kg/day palmitic acid to rats resulted in lipogranulomas observed in fat associated with the testis or ovary; this lesion was reversible upon diet substitution and attributed to dietary imbalance. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of 25 and 50 mg palmitic acid.[29]

Ricinoleic Acid None of 20 mice injected intravaginally with 2% ricinoleic acid (in gum tragacanth) had neoplasms or hyperplastic lesions of the corpus uteri, cervix uteri, vagina, or perineal skin. However, benign lung adenomas were observed in 10 of the 13 mice dosed with ricinoleic acid and in 6 of the 24 vehicle control mice that were killed after the 14th month of dosing.[30]

Stearic Acid Feeding of up to 50 g/kg/day dietary stearic acid to mice was not carcinogenic. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of up to 82 mg stearic acid.[29]

IRRITATION AND SENSITIZATION

Irritation

Skin

Non-Human

Acetamide MEA

Acetamide MEA, applied neat, was a mild skin irritant in an open-patch Draize test in 12 rabbits. In another study, acetamide MEA (70% active, minimum) was not a primary irritant when applied to the intact and abraded skin of rabbits using a 24-h occlusive patch.

From The Final Report on the Safety Assessment of Acetamide MEA[2]

Cocamide MEA

The irritancy potential of 50% cocamide MEA in petrolatum was evaluated in a 24-h patch test in guinea pigs, rabbits, and hairless mice. Cocamide MEA was slightly irritating to rabbits, but was not irritating to guinea pigs and hairless mice.

From The Final Report on the Safety Assessment of Cocamide MEA[3]

The irritation potential of cocamide MEA was evaluated in rabbits.[20] Cocamide MEA, 25%, was not irritating to rabbits when applied under an occlusive patch for 24 h. (Additional details were not provided.)

Lauramide MEA

In a Draize study, lauramide MEA was not irritating to rabbit skin.[21] No details were provided.

Stearamide MEA

The primary irritation index of a formulation containing 17.0% stearamide MEA was 1.00/8 in a group of 3 rabbits.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[1]

Human

Acetamide MEA

In a dermal irritation study using 19 female subjects, a formulation containing 0.5% acetamide MEA did not evoke unacceptable clinical irritation and was comparable to the control product.
From The Final Report on the Safety Assessment of Acetamide MEA[2]

Cocamide MEA

Cocamide MEA, 50% in petrolatum, was not irritating when a single 24-h patch was applied to the arm of 4 subjects.
From The Final Report on the Safety Assessment of Cocamide MEA[3]

Stearamide MEA

In a single-insult occlusive patch test of a 1% aq. solution of a formulation containing 17% stearamide MEA completed with 19 subjects, 7 subjects had questionable reactions and 3 subjects had mild reactions. In a 21-day, 14-subject, cumulative irritation study in which 0.2 ml of a formulation containing 5.0% stearamide MEA was applied using occlusive patches, slight irritation was observed, with a composite total score of 156/882.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[1]

Sensitization

Non-Human

Acetamide MEA

Acetamide MEA was not a sensitizer in a maximization study using 10 guinea pigs. Induction included an intradermal injection of 5.0% acetamide MEA in propylene glycol and in Freund's complete adjuvant and a topical application of 10% acetamide MEA.
From The Final Report on the Safety Assessment of Acetamide MEA[2]

Cocamide MEA

Cocamide MEA was not a sensitizer in a guinea pig maximization study. Details were not provided.[20]

Human

Acetamide MEA

In a 50-subject study, an aq. solution of 7.5% acetamide MEA did not cause primary irritation or sensitization. In a repeated insult patch test (RIPT) of a hair product containing 1.3% acetamide MEA, completed with 111 subjects, 12 subjects had mild reactions during induction and 2 of those subjects had mild reactions during challenge. However, the researchers concluded that a hair product containing 1.3% acetamide MEA was not a sensitizer.
From The Final Report on the Safety Assessment of Acetamide MEA[2]

Stearamide MEA

In an RIPT using 100 subjects in which 0.1 ml a formulation containing 5.27% stearamide MEA was applied using occlusive patches, the formulation did not produce sensitization.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[1]

Ocular Irritation

Non-Human

Acetamide MEA

Acetamide MEA (70% minimum activity) was practically non-irritating to the eyes of rabbits, and two hair formulations containing 1.3% acetamide MEA were not irritating to rabbit eyes.
From The Final Report on the Safety Assessment of Acetamide MEA[2]

Lauramide MEA

In a Draize ocular irritation study, Lauramide MEA was highly irritating to rabbit eyes.[21] Details were not provided.

Stearamide MEA

A formulation containing 5.27% stearamide MEA was not irritating to rabbit eyes. Minimal irritation was reported in one study with a formulation containing 17.0% stearamide MEA, while moderate irritation was reported in another.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[1]

SUMMARY

This report assesses the safety of 28 ethanolamides. This safety assessment originated as a re-review of isostearamide MEA, myristamide MEA, and stearamide MEA, and was expanded to include additional related ingredients. Some of

these ingredients have been previously reviewed by the CIR, and are included here to create a report on the complete family of ingredients.

Amidases, such as fatty acid amide hydrolase which is known to be present in human skin, could potentially convert the ethanolamides to ethanolamine and the corresponding fatty acids. The yield of ethanolamine from metabolism of ethanolamides in human skin is unknown. Secondary amides do tend to react with nitrosating agents to form nitrosamides. Impurity data were available for acetamide, myristamide, and stearamide MEA: acetamide MEA contained up to 0.0029% ethanolamine, 0.0030% acetamide, and no *N*-nitrosodiethanolamine; myristamide contained a maximum of 1.5% ethanolamine; and stearamide MEA contained up to 2.0% free amine (as ethanolamine).

Most of the ethanolamides are reported to function in cosmetics as hair conditioning agents, skin conditioning agents, and surfactant – foam boosters; a few are reported to have other uses . In 2011, stearamide MEA was reported to have only 10 uses, myristamide MEA had one, and isostearamide had none. Cocamide MEA has the highest frequency of use with 1122 reported uses; only 33 of those uses are in leave-on products. Cocamide MEA is reported to be used at up to 18% in rinse-off formulations and at up to 5% in leave-on formulations. Stearamide MEA has the highest concentration of use in leave-on formulations at up to 15%. In Europe, monoalkylamines, monoalkanolamines, and their salts are on the list of substances which must not form part of the composition of cosmetic products, except subject to restrictions and conditions laid down. Acetamide MEA and babassuamide MEA are included in this list. These restrictions include a maximum secondary amines contaminant content of 0.5% in finished products, a maximum secondary amines content of 0.5% in raw materials, and a maximum nitrosamine content of 50 µg/kg.

In an acute dermal study in rabbits, the LD_{50} for cocamide MEA was > 2g/kg and for acetamide MEA, it was >20 ml/kg; these were the highest doses tested. In oral studies, the LD_{50} of cocamide MEA was >5 g/kg in rats and >10 g/kg in mice. The oral LD_{50} values in rats for acetamide and lauramide MEA were 27 g/kg and >2 g/kg, respectively. In repeated dose dermal studies, acetamide MEA (50%; 13 wks in rabbits), cocamide MEA (25%; 1 wk in mice), and stearamide MEA (10% solution of a formulation containing 17% in rabbits, applied for 4 wks; 5.27% in rats, applied for 13 wks) were not toxic. In a 14-day oral study, the NOAEL of cocamide MEA in rats was >750 mg/kg/day, the highest dose tested.

No data on the reproductive and developmental toxicity or carcinogenicity of ethanolamides were found. Available data from previous CIR reports on ethanolamine and some of the substituents were summarized, and no significant toxic effects were noted.

Acetamide MEA (≤5000 µg/plate), cocamide MEA (≤2500 µg/plate) and lauramide MEA (≤3333 µg/plate) were not mutagenic in Ames test with or without metabolic activation. Acetamide MEA did not induce unscheduled DNA synthesis in primary rat hepatocytes.

Acetamide MEA was at most a mild skin irritant in rabbits, and in humans, a formulation containing 0.5% acetamide MEA was not an irritant. Cocamide MEA was, at most, slightly irritating to rabbit skin, and it was not irritating to guinea pigs and hairless mice. In clinical testing, 50% cocamide MEA in petrolatum was not irritating. A formulation containing 17% stearamide MEA had a primary irritation score of 1/8 in rabbits, and in a clinical single-insult occlusive patch test, a 1% aq. solution of this formulation produced questionable reactions is 7 and mild reactions in 3 of 19 subjects; in a clinical cumulative irritation study, 5% stearamide MEA produced slight irritation. Acetamide MEA and cocamide MEA were not sensitizers in guinea pigs. In clinical testing, a solution of 7.5% acetamide MEA, a formulation containing 1.3% acetamide MEA, and a formulation containing 5.27% stearamide MEA were not sensitizers.

Acetamide MEA (70% minimum activity) was practically non-irritating to rabbit eyes, and formulations containing 1.3% acetamide MEA and 5.27% stearamide MEA were not irritating to rabbit eyes. A formulation containing 17% stearamide MEA was a moderate ocular irritant and lauramide MEA was highly irritating to rabbit eyes.

DISCUSSION

Isostearamide MEA, myristamide MEA, and stearamide MEA, along with acetamide MEA and cocamide MEA, previously have been reviewed by the CIR Expert Panel. This amended safety assessment includes those five ingredients and 23 additional ethanolamides that are also secondary carboxamides comprised of the amidation products of alkyl carboxylic acids and ethanolamine. This amended safety assessment originated as a re-review of ethanolamides, and was expanded to include additional ethanolamides, the safety of which was supported by the data available in the original safety assessment and by other published and unpublished studies.

The Panel noted gaps in the available safety data for other endpoints for many of the ethanolamides included in this group. Because these ingredients are secondary amides, whereby one of the nitrogen substituents is ethanol and the second is a carbonyl attached substituent, their chemical structures are similar, their structure/activity relationships are expected to be similar, and their functions in cosmetics are similar, supporting use of the available data to support the safety of all the ethanolamides included in this safety assessment.

Published toxicokinetics data are lacking, as are reproductive and developmental toxicity and carcinogenicity data. However, the Panel was of the opinion that dermal penetration would be limited based on the size and the lipophilicity of

these ethanolamides. Based on the totality of the data set, the Panel did not think these ingredients would have reproductive or carcinogenic effects.

Also, while it is a metabolic possibility that amidases present in human skin could potentially convert the ethanolamides to ethanolamine and the corresponding acid, such potential amidase activity would at most cleave a small fraction of the applied ethanolamides. If these ethanolamides were cleaved into ethanolamine and the respective acids, the substantial data available on ethanolamine and other substituents indicate that these components do not have reproductive or carcinogenic effects.

Because it could be possible that diethanolamine may exist as an impurity, the Panel re-iterated its discussion regarding the positive findings reported in a dermal carcinogenicity study of diethanolamine. The hepatocarcinogenicity that was reported in mice was considered to have little relevance to the safety of diethanolamine in personal care products. Additionally, renal lesions reported in mice could have been the result of diethanolamine-induced choline deficiency, a mechanism that has little relevance in humans. If diethanolamine-induced choline deficiency was not the cause of the renal lesions, it was thought there was still no carcinogenic risk to humans because diethanolamine does not appear to penetrate human skin to any significant extent at concentrations relevant to human exposures from the use of personal care products.

The ethanolamides consist of covalent, secondary amides. The Panel was concerned secondary amides tend to react with nitrosating agents to form nitrosamides. Because of the potential for this process to occur, ethanolamides should not be used in cosmetic products in which N-nitroso compounds may be formed.

The potential exists for dermal irritation with the use of products formulated using ethanolamides. The Panel specified that products containing ethanolamides must be formulated to be non-irritating. Test data indicate that these ingredients are not sensitizers.

Acetamide MEA is used at up to 0.4% in aerosol hair sprays and cocamide MEA and lauramide MEA are used at up to 1% in foot sprays. Because of these uses, the Panel discussed the issue of incidental inhalation exposure. In the absence of inhalation data, the Panel considered other pertinent data that were available, including, e.g., data characterizing the potential for ethanolamides to cause systemic toxicity, ocular irritation, and dermal irritation or sensitization. The Panel also noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

CONCLUSION

The CIR Expert Panel concluded that the ethanolamides listed below are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating. The Expert Panel cautioned that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

Acetamide MEA
Azelamide MEA*
Babassuamide MEA*
Behenamide MEA*
C16-22 Acid Amide MEA*
Cocamide MEA
Cocamide Methyl MEA
Cocamidopropyl Betainamide MEA Chloride
Hydroxystearamide MEA*
Isostearamide MEA*
Lactamide MEA
Lauramide MEA
Linoleamide MEA*
Myristamide MEA
Oatamide MEA*
Oleamide MEA*
Oliveamide MEA*
Palm Kernelamide MEA*
Palmamide MEA*
Palmitamide MEA*
Pantothenamide MEA*
Peanutamide MEA
Ricinoleamide MEA
Stearamide MEA
Sunfloweramide MEA*
Tallowamide MEA*
Trideceth-2 Carboxamide MEA
Undecylenamide MEA

Were the ingredients not in current use (as indicated by *) 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 and structures

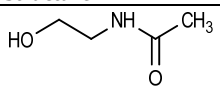
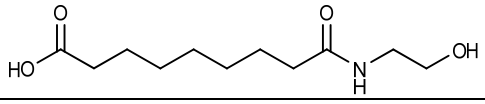
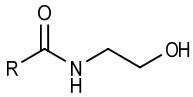
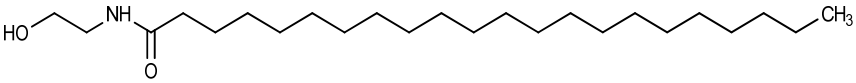
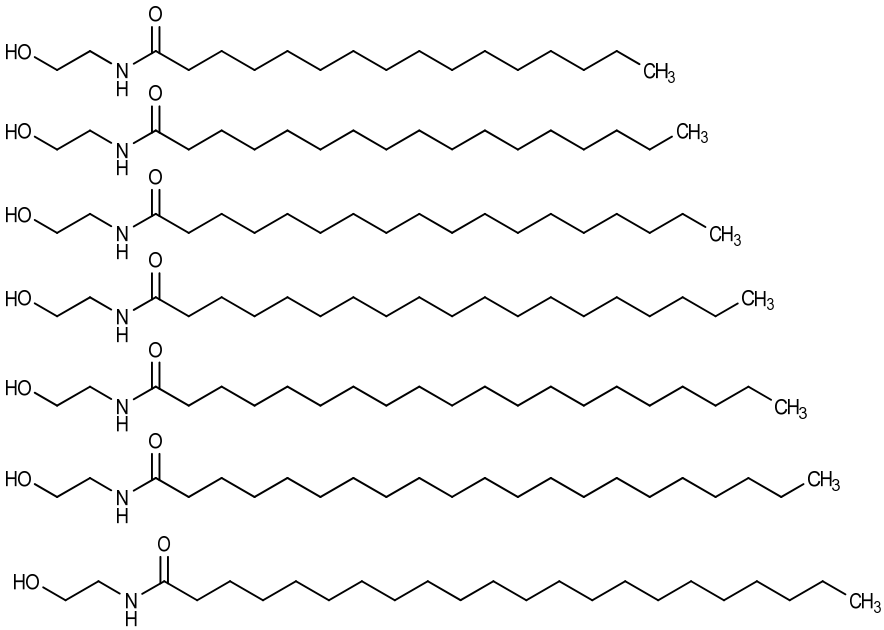
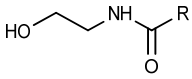
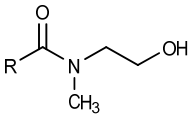
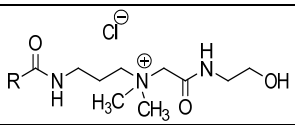
Ingredient; CAS No.	Definition	Reported Function[10]	Structure
Acetamide MEA 142-26-7	the ethanolamide of acetic acid	hair cond. ag.; skin cond. ag.-humectant; surf.-foam booster; visc. incr. ag.-aq.	
Azelamide MEA	the ethanolamide of azelaic acid	surf.-foam booster; vis. incr. ag-aq.	
Babassuamide MEA 69227-24-3	a mixture of ethanol-amides of the fatty acids derived from Orbignya oleifera (babassu) oil.	hair cond ag; surf-foam booster; surf-solublilizing ag; visc. incr. ag.-aq.	 wherein  represents the fatty acid residues of babassu oil
Behenamide MEA 94109-05-4	the ethanolamide of behenic acid	hair cond ag.	
C16-22 Acid Amide MEA	a mixture of ethanol-amides of C16-22 fatty acids	surf-cleansing ag.	
Cocamide MEA 68140-00-1	a mixture of ethanol-amides of Cocos nucifera (coconut) acid	surf.-foam booster; visc. incr. ag.-aq.	 wherein  represents the fatty acid residues of coconut acid
Cocamide Methyl MEA	a mixture of tertiary, *N*-methyl ethanolamides of the fatty acids derived from Cocos Nucifera (Coconut) Oil	surf.-foam booster; visc. controlling ag.	 wherein  represents the fatty acid residues of coconut oil
Cocamidopropyl Betain-amide MEA Chloride 164288-56-6	a mixture of *N'*-betaine ethanolamides of the fatty acids derived from coconut oil	surf.-cleans. agent; surf.-foam booster	

Table 1. Definitions and structures

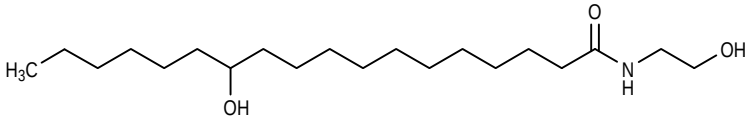
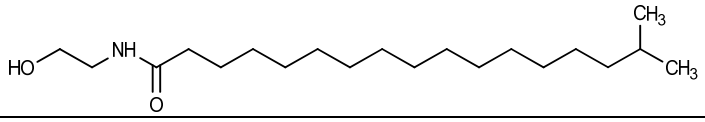
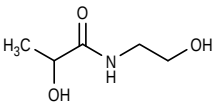
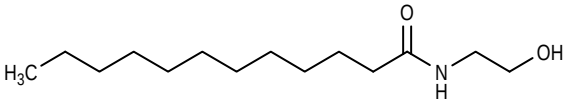
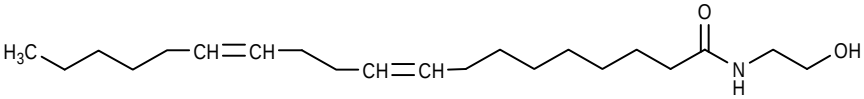
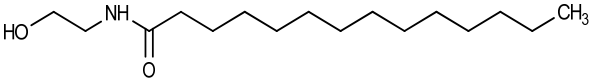
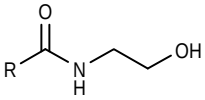
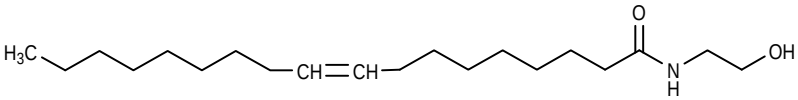
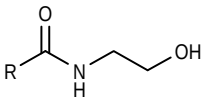
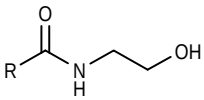
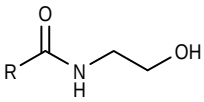
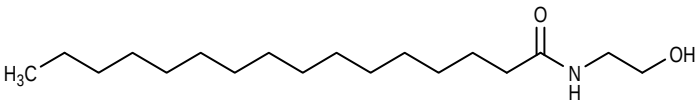
Ingredient; CAS No.	Definition	Reported Function[10]	Structure
Hydroxystearamide MEA 106-15-0	the 12-hydroxy substituted derivative of stearamide MEA	surf.-foam booster; visc. incr. ag.-aq.	
Isostearamide MEA 54536-43-5	the ethanolamide of isostearic acid	surf.-foam booster; visc. incr. ag.-aq.	one example of an "iso" 
Lactamide MEA 5422-34-4	the ethanolamide of lactic acid	hair cond. ag.; skin cond. ag.-humectant; surf.-foam booster; vis. incr. ag.-aq.	
Lauramide MEA 142-78-9	the ethanolamide of lauric acid	surf.-foam booster; visc. incr. ag.-aq.	
Linoleamide MEA 10015-67-5	the ethanolamide of linoleic acid	hair cond. ag.; surf.-foam booster; visc. incr. ag.-aq.	
Myristamide MEA 109-83-1	the ethanolamide of myristic acid	surf-foam booster; visc. incr. ag.-aq.	
Oatamide MEA	a mixture of ethanolamides of the fatty acids derived from oat kernel oil	surf.-foam booster; visc. incr. ag.-aq.	 where RCO- represents the fatty acids derived from Avena Sativa (Oat) Kernel Oil
Oleamide MEA 111-58-0	the ethanolamide of oleic acid	surf.-foam booster; visc. incr. ag.-aq.	
Oliveamide MEA	a mixture of ethanolamides of the fatty acids derived from olive oil.	hair cond. ag.; surf.-foam booster; surf.-solubilizing ag.; visc. incr. ag.-aq.	 where RCO- represents the fatty acids derived from olive oil
Palm Kernelamide MEA	a mixture of ethanolamides of the fatty acids derived from Elaeis guineensis (palm) kernel oil	surf.-foam booster; visc. incr. ag.-aq.	 where RCO- represents the fatty acids derived from palm kernel oil
Palmamide MEA	a mixture of ethanolamides of the fatty acids derived from Elaeis guineensis (palm) oil	surf.-foam booster; visc. incr. ag.-aq.	 where RCO- represents the fatty acids derived from palm oil
Palmitamide MEA 544-31-0	the ethanolamide of palmitic acid	surf.-foam booster; visc. incr. ag.-aq.	

Table 1. Definitions and structures

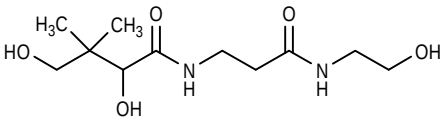
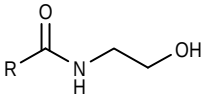
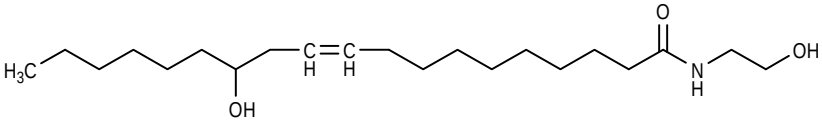
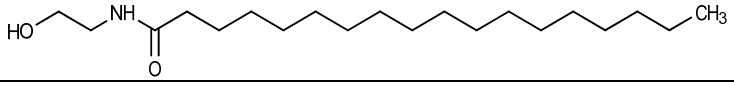
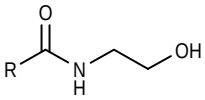
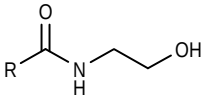
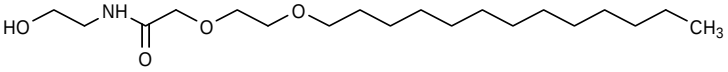
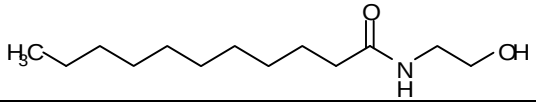
Ingredient; CAS No.	Definition	Reported Function[10]	Structure
Pantothenamide MEA	the O-monoethylene-glycol substituted derivative pantothen-amide MEA	skin cond. ag.-misc.	
Peanutamide MEA	a mixture of ethanola-mides of the fatty acids derived from Arachis hypogaea (peanut) oil	surf.-foam booster; visc. incr. ag.-aq.	 where RCO- represents the fatty acids derived from peanut oil
Ricinoleamide MEA 106-16-1 75033-33-9	the ethanolamide derived from ricinoleic acid	surf.-foam booster; visc. incr. ag.-aq.	
Stearamide MEA 111-57-9	the ethanolamide of stearic acid	surf-foam booster; visc, incr. ag. - aq	
Sunfloweramide MEA 69227-24-3	a mixture of ethanola-mides of the fatty acids derived from Helianthus annuus (sunflower) seed oil	surf.-cleans. ag.; surf.-foam booster; visc. controlling ag.; visc. incr. ag.-aq..	 where RCO- represents the sunflower seed oil fatty acids
Tallowamide MEA 68440-25-5	a mixture of ethanol-amides of tallow acid	surf.-foam booster; visc. incr. ag.-aq.	 where RCO- represents the fatty acids derived from tallow
Trideceth-2 Carboxamide MEA 107628-04-6	the ethanolamide of trideceth-2	hair cond, ag.; surf.-foam booster; visc. incr. ag.-aq.	
Undecylenamide MEA 20545-92-0 75046-17-2	the ethanolamide of undecylenic acid	hair cond. ag.; surf.-foam booster; visc. incr. ag.-aq.	

Table 2. Conclusions of previously reviewed ingredients and substituents

Ingredient	Conclusion
	PREVIOUSLY REVIEWED INGREDIENTS
Isostearamide MEA	safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 17% (1995)[1]
Myristamide MEA	safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 17% (1995)[1]
Stearamide MEA	safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 17% (1995)[1]
Acetamide MEA	safe as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products; safe in the present practices of use in rinse-off products; products containing acetamide MEA should not contain nitrosating agents or significant amounts of acetamide (1993)[2]
Cocamide MEA	safe as used in rinse-off products; safe at concentrations up to 10% in leave-on products; should not be used as an ingredient in products containing *N*-nitrosating agents, or **in product formulations intended to be aerosolized** (1999)[3]
	SUBSTITUENTS
Ethanolamine (likely an impurity)	safe as used when formulated to be non-irritating; should not be used in cosmetic products in which N-nitroso compounds may be formed (2011)[31]
Arachis Hypogaea (Peanut) Oil	safe as used (2011)[32]
Avena Sativa (Oat) Kernel Oil	safe as used (2011)[32]
Azelaic Acid	safe as used (2010)[33]
Cocamidopropyl Betaine	safe as used when formulated to be non-sensitizing (2010)[27]
Coconut Acid	safe as used (2008) [34]
Elaeis Guineensis (Palm) Kernel Oil Elaeis Guineensis (Palm) Oil	safe as used (2011)[32]
Helianthus Annuus (Sunflower) Seed Oil	safe as used (2011)[32]
Hydroxystearic Acid	safe as used (1999)[24]
Isostearic Acid	safe as used (1983)[35]
Lactic Acid	safe for use in cosmetic products at concentrations ≤10%, at final formulation pH > 3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations ≤ 30%, at final formulation pH ≥3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection (1998)[28]
Lauric Acid	safe as used (1987)[29]
Myristic Acid	safe as used (1987)[29]
Olea Europaea (Olive) Fruit Oil	safe as used (2011)[32]
Oleic Acid	safe as used (1987)[29]
Orbignya Oleifera (Babassu) Oil	safe as used (2011)[32]
Palmitic Acid	safe as used (1987)[29]
Pantothenic Acid	safe as used (1987)[36]
Ricinoleic Acid	safe as used (2007)[30]
Stearic Acid	safe as used (1987)[29]
Trideceth-2	safe as used when formulated to be non-irritating (2010)[37]

Table 3. Physical and chemical properties

Property	Value	Reference
	Acetamide MEA	
Molecular Weight	103.12 (calculated)	38
pKa	14.56 g/cm^3 (most acidic; 25°C) -0.65 g/cm^3 (most basic; 25°C) (calculated)	38
Density	1.115 g/cm^3 (25°C) (calculated)	39
Melting Point	63-64°C	40
Boiling Point	195-196°C	39
log P	-1.336 (25°C) (calculated)	38
	Behenamide MEA	
Molecular Weight	383.65 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.896 g/cm^3 (20°C) (calculated)	38
log P	8.853 (25°C) (calculated)	38
	C16-22 Acid Amide MEA	
Molecular Weight	117.19 (calculated)	38
pKa	14.81 g/cm^3 (most acidic; 25°C) 9.90 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.875 g/cm^3 (20°C) (calculated)	38
Melting Point	-2°C	41
Boiling Point	199°C	41
log P	0.467 (25°C) (calculated)	38
	Cocamide MEA	
Melting Point	~72°C	20
Density	~0.894 g/cm^3 (80°C)	20
log P	3.89 (calculated)	20
Solubility	not soluble in water	20
	Hydroxystearamide MEA	
Molecular Weight	343.54 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.954 g/cm^3 (20°C) (calculated)	38
Melting Point	106.5-108°C	42
Boiling Point	522.4°C (calculated)	38
log P	4.753 (25°C) (calculated)	38
	Lauramide MEA	
Physical Form	solid	19
Molecular Weight	243.39	19
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.925 g/cm^3 (20°C) (calculated)	38
Melting Point	89-91°c	43
Boiling Point	410.7°C (calculated)	38
Water Solubility	miscible with water	19
log P	3.758 (25°C) (calculated)	38
	Linoleamide MEA	
Molecular Weight	323.51 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.926 g/cm^3 (20°C) (calculated)	38
Boiling Point	499.1°C (calculated)	38
log P	6.003 (25°C) (calculated)	38
	Myristamide MEA	
Molecular Weight	271.44 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.916 g/cm^3 (20°C) (calculated)	38
Melting Point	93-94°C	44
Boiling Point	436.3°C (calculated)	38
log P	4.777 (25°C) (calculated)	38
	Oleamide MEA	
Molecular Weight	325.53 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.915 g/cm^3 (20°C) (calculated)	38
Melting Point	63-64°C	43
Boiling Point	496.4°C (calculated)	38
log P	6.406 (25°C) (calculated)	38

Table 3. Physical and chemical properties

Property	Value	Reference
	Palmitamide MEA	
Molecular Weight	299.49 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.910 g/cm^3 (20°C) (calculated)	38
Melting Point	98°C	45
Boiling Point	461.5°C (calculated)	38
log P	5.796 (25°C) (calculated)	38
	Ricinoleamide MEA	
Molecular Weight	341.53 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.965 g/cm^3 (20°C) (calculated)	38
Melting Point	58-59°C	42
Boiling Point	536.2°C (calculated)	38
log P	4.592 (25°C) (calculated)	38
	Stearamide MEA	
Molecular Weight	327.55 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.904 g/cm^3 (20°C) (calculated)	38
Melting Point	106-108°C	43
Boiling Point	486.0°C (calculated)	38
log P	6.815 (25°C) (calculated)	38
	Undecylenamide MEA	
Molecular Weight	227.34 (calculated)	38
pKa	14.49 g/cm^3 (most acidic; 25°C) -0.67 g/cm^3 (most basic; 25°C) (calculated)	38
Density	0.940 g/cm^3 (20°C) (calculated)	38
Melting Point	56-58°C	46
Boiling Point	409.4°C (calculated)	38
log P	2.841 (25°C) (calculated)	38

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

	# of Uses[11]	*Max. Conc. of Use (%)*[12]	*# of Uses*[11]	*Max. Conc. of Use (%)*[12]	*# of Uses*[11]	*Max. Conc. of Use (%)*[12]
	Acetamide MEA		**Cocamide MEA**		**Cocamide Methyl MEA**	
Totals*	**148**	**0.03-8**	**1122**	**0.2-18**	**NR**	**5**
Duration of Use						
Leave-On	*64*	*0.03-8*	*33*	*0.5-5*	*NR*	*NR*
Rinse-Off	*84*	*0.06-5*	*1008*	*0.2-18*	*NR*	*5*
Diluted for (Bath) Use	*NR*	*NR*	*81*	*2-6*	*NR*	*NR*
Exposure Type						
Eye Area	1	0.5	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	14	0.1-0.4	3[b]	0.7[b]; 1	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	25	0.03-8	579	0.2-10	NR	NR
Deodorant (underarm)	9[a]	2[a]	NR	NR	NR	NR
Hair - Non-Coloring	121	0.06-5	367	1-15	NR	5
Hair-Coloring	1	NR	173	3-18	NR	NR
Nail	1	NR	2	NR	NR	NR
Mucous Membrane	3	3-4	521	1-10	NR	NR
Baby Products	NR	NR	4	2	NR	NR

	Cocamidopropyl Betainamide MEA Chloride		**Lactamide MEA**		**Lauramide MEA**	
Totals*	**21**	**1-3**	**27**	**0.02-3**	**87**	**0.3-4**
Duration of Use						
Leave-On	*NR*	*NR*	*21*	*0.02-2*	*3*	*0.5-4*
Rinse Off	*21*	*1-3*	*6*	*0.2-3*	*80*	*0.3-3*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*2*	*4*	*2*
Exposure Type						
Eye Area	NR	NR	1	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	4	0.02-0.2	1	1
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	21	1-3	9	2-3	35	0.3-4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	17	0.02-3	9	1-3
Hair-Coloring	NR	NR	NR	NR	43	3
Nail	NR	NR	1	NR	NR	1
Mucous Membrane	18	1-3	1	2-3	28	1-3
Baby Products	NR	NR	NR	NR	NR	0.5

	Myristamide MEA		**Peanutamide MEA**		**Ricinoleamide MEA**	
Totals*	**1**	**0.3-4**	**NR**	**0.3**	**NR**	**0.02**
Duration of Use						
Leave-On	*NR*	*4*	*NR*	*NR*	*NR*	*NR*
Rinse-Off	*1*	*0.3*	*NR*	*0.3*	*NR*	*0.02*
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	1	0.3-4	NR	0.3	NR	0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

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

	# of Uses[11]	*Max. Conc. of Use (%)*[12]	*# of Uses*[11]	*Max. Conc. of Use (%)*[12]	*# of Uses*[11]	*Max. Conc. of Use (%)*[12]
	Stearamide MEA		**Trideceth-2 Carboxamide MEA**		**Undecylenamide MEA**	
Totals	**10**	**0.07-17**	**189**	**2-14**	**3**	**NR**
Duration of Use						
Leave-On	*2*	*2-15*	*NR*	*2*	*2*	*NR*
Rinse Off	*8*	*0.07-6*	*189*	*2-14*	*1*	*NR*
Diluted for (Bath) Use	*NR*	*17*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	6-7	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	1	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	3	0.2-15	1	NR	2	NR
Deodorant (underarm)	2[a]	15[a]	NR	NR	1[a]	NR
Hair - Non-Coloring	NR	0.07	5	2	NR	NR
Hair-Coloring	7	2-6	183	4-14	1	NR
Nail	NR	2	NR	NR	NR	NR
Mucous Membrane	NR	17 (diluted prior to use)	1	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses.
[a] It is not known whether or not the product is a spray.
[b] Includes suntan products, in that it is not known whether or not the reported product is a spray.
NR – no reported uses

Table 4b. Not reported to be in use

Azelamide MEA
Babassuamide MEA
Behenamide MEA
C16-22 Acid Amide MEA
Hydroxystearamide MEA
Isostearamide MEA
Linoleamide MEA
Oatamide MEA
Oleamide MEA
Oliveamide MEA
Palm Kernelamide MEA
Palmamide MEA
Palmitamide MEA
Pantothenamide MEA
Sunfloweramide MEA
Tallowamide MEA

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Data

FINAL REPORT

Isostearamide DEA & MEA
Myristamide DEA & MEA
Stearamide DEA & MEA
Acid

ABSTRACT

Stearamide DEA & MEA, Isostearamide DEA & MEA, and Myristamide DEA & MEA are all ethanolamides of fatty acids that function as foam boosting surfactants and aqueous viscosity increasing agents in cosmetic products. All except Myristamide MEA are currently used in cosmetic formulations. The maximum concentration of use for these ingredients is 15% in anti-perspirants. There is little data available on toxicity of these ethanolamides. The limited clinical tests show some irritation with formulations containing Stearamide MEA, but no sensitization. Data are available on DEA & MEA and on the fatty acids, however, and these are summarized in this report. The principle toxicity concern is for the ethanolamines, DEA & MEA. Dermal and ocular irritation have been reported, and there is the potential for nitrosation in the presence of N-nitrosating agents. These data were previously reviewed with the conclusion that concentration and other limits are needed to assure their safe use in cosmetic formulations. Estimates of the amounts of ethanolamines that may be released on hydrolysis of Stearamide DEA & MEA, Isostearamide DEA & MEA, and Myristamide DEA & MEA were made and generally expected to be below the concentration limit of 5% previously established. Because only certain concentrations of Stearamide DEA & MEA, Isostearamide DEA & MEA, and Myristamide DEA & MEA were actually tested clinically, these concentrations were considered as the maximum values for which safety could be concluded. On the basis of the available information, it was concluded that Stearamide DEA & MEA, Isostearamide DEA & MEA, and Myristamide DEA & MEA are safe for use in rinse-off products. In leave-on products, it was concluded these ingredients are safe for use at concentrations that limit the release of free ethanolamines to 5%, but that the maximum concentration of Stearamide MEA, Isostearamide MEA, and Myristamide MEA should be 17% and the maximum concentration of Stearamide DEA, Isostearamide DEA, and Myristamide DEA should be 40%. In addition, it was concluded that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

INTRODUCTION

The following report is a review of the safety data on Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA, which are used in cosmetics as foam boosting surfactants and as aqueous viscosity increasing agents. Chemically, these ingredients are the ethanolamides of Isostearic, myristic, and stearic acid. These basic components were reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel and Final Reports have been published (Elder, 1983a; Elder, 1983b; Elder, 1987). The following conclusions were made by the Expert Panel:

<u>Triethanolamine (TEA),Diethanolamine (DEA) and, Monoethanolamine (MEA)</u> are safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, the concentration of ethanolamines should not exceed 5%. MEA should be used only in rinse-off products. TEA and DEA should not be used

in products containing N-nitrosating agents (Elder, 1983a).

Isostearic, Myristic, and Stearic Acids are safe in the present practices of use and concentration in cosmetics (Elder, 1983b; Elder, 1987).

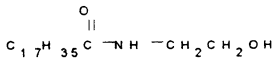
Since there are limited safety data specifically on Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA, the relevant data from the Final Reports on TEA, DEA, MEA, and Isostearic, myristic, and stearic acid have been extracted and summarized in this review as a basis for the assessment of safety of these six ingredients.

The Expert Panel has reviewed other diethanolamides of fatty acids, specifically Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA (Elder, 1986). These ingredients were found to be safe for use as cosmetic ingredients, with the caveat that they should not be used in products containing nitrosating agents. Summaries of the data used to reach this conclusion are included at the end of this report.

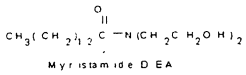
CHEMISTRY

Definition and Structure

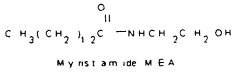
Isostearamide DEA (CAS No. 52794-79-3) and Isostearamide MEA (CAS No. 54536-43-5) are mixtures of ethanolamides of Isostearic Acid (q.v.). Isostearamide DEA has the empirical formula: C22H45NO3, and Isostearamide MEA conforms to the following formula (Wenninger and McEwen, 1993):



Myristamide DEA (CAS No. 7545-23-5) and Myristamide MEA (CAS No. 142-58-5) are mixtures of ethanolamides of myristic acid conforming to the formulas (Wenninger and McEwen, 1993):

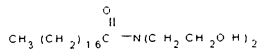


Myristamide DEA

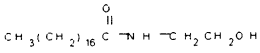


Myristamide MEA

Stearamide DEA (CAS No. 93-82-3) and Stearamide MEA (CAS No. 111-57-9) are mixtures of ethanolamides of stearic acid that conform to the following formulas (Wenninger and McEwen, 1993):



Stearamide DEA



Stearamide MEA

Chemical and Physical Properties

Myristamide DEA is a white to off-white waxy solid that is a condensation product of myristic acid and diethanolamine. It is soluble in alcohol, chlorinated hydrocarbons and aromatic hydrocarbons and is dispersible in water, mineral spirits, kerosene, white mineral oils, and natural fats and oils. A 10% aq. dispersion of Myristamide DEA has a pH range of 9.5 to 10.5. This ingredient has a melting range of 40-54°C, an alkali value of 26-50, and a maximum acid value of 1 (Nikitakis and McEwen, 1990).

Myristamide MEA is a pale straw to tan colored wax with a faintly soapy odor. It is soluble in water and a 1% aq. solution has a pH range of 8.0-10.0. The melting range of this ingredient is 89-93°C, the maximum acid value is 7.0, the maximum free amine is 1.5%, and the maximum moisture is 0.7% (Nikitakis and McEwen, 1990).

Stearamide DEA is a white to pale yellow, wax-like solid. It is dispersible in water and is soluble in most organic solvents. The pH range of a 1% aq. dispersion ranges from 9 to 10. This compound is characterized by 9-12% free fatty acids (as oleic acid) and 2-6% free amines (as diethanolamine). The maximum amount of moisture for this compound is 1.5%, and the maximum amounts of arsenic and lead are

3 ppm and 20 ppm, respectively (Nikitakis and McEwen, 1990).

Stearamide MEA is also a wax-like solid, with a white to cream color. It has a faint characteristic odor and is soluble in hot alcohol, chlorinated solvents, fats and oils, and is dispersible in water. A 10% aq. dispersion has a pH range of 9.0 to 10.5. The melting point of this ingredient is 86-90°C. It has 0.8% maximum free fatty acids (as stearic acid), 0.5-2.0% free amine (as monoethanolamine), and 54.0-58.0% total fatty acids (as stearic acid). The acid value of separated fatty acids is 200-210. The maximum moisture value is 0.5, and the maximum amounts of arsenic and lead are 3 ppm and 20 ppm, respectively (Nikitakis and McEwen, 1990).

Analytical Methods

Stearamide MEA and DEA can be separated using high-performance liquid chromatography by employing a porous micro-spherical poly(styrene-divinylbenzene) gel as the stationary phase (Nakae and Kunihiro, 1978).

USE

Cosmetic

United States

Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA are used as a foam boosting surfactants and as aqueous viscosity increasing agents in cosmetic formulations (Wenninger and McEwen, 1992). The product formulation data submitted to the Food and Drug Administration (FDA) in 1995 reported that Isostearamide DEA was used in 23 products, Isostearamide MEA in one product, Myristamide DEA in six products, Stearamide DEA in 19 products, and Stearamide MEA in 22 products. There was no listing for Myristamide MEA (Table 1) (FDA, 1995).

The concentrations at which these ingredients are used are unknown because concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, data submitted to CIR by the Cosmetic, Toiletry, and Fragrance Association [CTFA] reported that Isostearamide DEA, Myristamide DEA, and Stearamide DEA and MEA are used in anti-perspirants at a concentration of 15%, in shampoos at a concentration of 6%, in shower gels at a concentration of 5%, and in perms and relaxers at a concentration of 2% (CTFA, 1995). Additionally, product formulation data submitted to the FDA in 1984 stated that Isostearamide DEA, Myristamide DEA, and Stearamide DEA were used at concentrations up to 10% and that Stearamide MEA was used at concentrations up to 25% (FDA, 1984).

International

Isostearamide DEA, Myristamide DEA, and Stearamide DEA and MEA are approved for use in Japan (Rempe and Santucci, 1992).

The European Union limits the use of fatty acid dialkanolamides to a maximum dialkanolamine content of 0.5% in finished products. These types of ingredients are not to be used with nitrosating systems. Maximum dialkanolamine content in raw material should not exceed 5%, and the maximum allowable N-nitrosodialkanolamine content is 50 µg/kg (EEC Cosmetics Directive, 1993).

BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

MEA is the only naturally occurring ethanolamine in mammals and is excreted in the urine. Much of the available scientific literature on the metabolism of the ethanolamines is concerned with the effect on phospholipid biosynthesis following intraperitoneal and

TABLE 1

COSMETIC PRODUCT FORMULATION DATA (FDA, 1995)

Product Category	Total No. Formulations in Category	Total No. of Formulations Containing Ingredient
	ISOSTEARAMIDE DEA	
Other bath preparations	144	3
Other eye makeup preparations	130	1
Shampoos (non-coloring)	916	3
Foundations	333	3
Makeup bases	159	3
Makeup fixatives	11	3
Other makeup preparations	155	2
Moisturizing	873	4
Other skin care preparations	782	1
1995 Total		**23**
	ISOSTEARAMIDE MEA	
Shampoos (non-coloring)	916	1
1995 Total		**1**
	MYRISTAMIDE DEA	
Other bath preparations	144	1
Shampoos (non-coloring)	916	4
Bath soaps and detergents	339	1
1995 Total		**6**
	STEARAMIDE DEA	
Hair conditioners	639	4
Shampoos (non-coloring)	916	1
Foundations	333	4
Makeup bases	159	1
Other makeup preparations	155	2
Cleansing preparations	771	1
Face and neck (excluding shaving preparations)	261	1
Body and hand (excluding shaving preparations)	987	3
Moisturizing	873	2
1995 Total		**19**

Product Category	Total No. Formulations in Category	Total No. of Formulations Containing Ingredient
	STEARAMIDE MEA	
Hair conditioners	693	6
Permanent waves	423	2
Hair dyes and colors (all types requiring caution statements and patch tests)	1437	8
Bath soaps and detergents	339	1
Deodorants (underarm)	293	1
Other personal cleanliness products	317	1
Cleansing preparations	771	2
Face and neck (excluding shaving preparations)	261	1
1995 Total		**22**

intracerebral administration of MEA to animals or in vitro effects on mammalian tissue. In general, it was documented that MEA was converted to phosphatidylethanolamine in all the tissues, and into phosphatidylcholine in some tissues Elder, 1983a).

In general, fatty acids are absorbed, digested, and transported in animals and humans. Radioactivity from labeled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph. ß-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl-CoA. Placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied. High intake of dietary saturated fatty acids has been associated with the incidence of atherosclerosis and thrombosis (Elder, 1987).

ANIMAL TOXICOLOGY

Oral Studies

Acute Toxicity

The oral LD50s of DEA and MEA for rats range from 0.71 ml/kg to 2.83 g/kg and 1.72 g/kg to 2.74 g/kg, respectively (Elder, 1983a).

In rats, the oral LD50 for Isostearic acid was estimated to be >32 ml/kg (Elder, 1983b). Little acute toxicity was observed in studies with myristic and stearic acid at concentrations up to 10 g/kg, or with cosmetic formulations containing stearic acid at concentrations of 2.8-13% at a dose of 15-19 g/kg body weight (Elder, 1987).

The oral LD50 of a mixture containing 35-40% Stearamide DEA was >20 g/kg for CFW mice (Leberco Laboratories, 1971a). For a formulation containing 17.0% Stearamide MEA, the LD50 for rats was >5.0 g/kg (CTFA, 1975a).

Short-Term Toxicity

In 2-wk toxicity studies, F344/N rats and B6C3F1 mice were given 630, 1250, 2500, 5000, and 10000 ppm DEA in drinking water. All female rats in the two highest dose groups and two male rats in the 10000 ppm group died before the end of the study. Surviving rats in the higher concentration groups had reduced weight gains. The following effects were also observed in dosed rats: poorly regenerative, microcytic anemia, increased kidney weights, renal tubular cell necrosis, and decreased renal function. Male rats also had degenerated seminiferous tubules of the testis. In studies with mice, there was a dose-dependent

increase in liver weight, and cytologic alteration and necrosis of individual hepatocytes were found in the highest dose group (NTP, 1992).

Subchronic and Chronic Toxicity

In subchronic oral studies with rats, DEA and MEA produced lesions limited mainly to the liver and kidneys. In general, DEA was more toxic to rats than MEA. It was suggested that this may be because MEA has a normal function in the lipid metabolism of the body and DEA is structurally similar enough to MEA to act in competition with it and interfere with lipid metabolism (Elder, 1983a).

In drinking water studies, rats were given 320-5000 ppm (males) or 160-2500 ppm (females) DEA, and mice were given 630-10000 ppm (males and females) DEA for 13 wks. Deaths occurred in the three highest dose groups of mice, and two rats in the high dose group also died. Reduced body weight gains occurred among the animals surviving the higher concentrations. Dosed rats had poorly regenerative, microcytic anemia, increased kidney weights, renal tubular cell necrosis, decreased renal function, increased incidences or severity of nephropathy, tubular necrosis, and mineralization. Male rats also had degenerated seminiferous tubules of the testis, and sperm motility and count were decreased. In both male and female rats, demyelination in the medulla oblongata and spinal cord were observed (NTP, 1992).

No toxic effects were observed in a two year study of dogs fed 0.0975% g/kg/day MEA (Elder, 1983a).

When stearic acid was tested in subchronic feeding studies with rats, doses ranging from 5-50% caused thrombosis, aortic atherosclerosis, anorexia, and mortality. Similar effects were observed in chronic feeding studies with rats at doses of 50 g/kg/day and 3000 ppm in the diet (Elder, 1987).

Dermal Studies

Acute Toxicity

Mild to moderate erythema but no edema was observed when rabbits were treated on both intact and abraded skin with undiluted (88.1% and 91.8% active) TEA (Elder, 1983a).

Intradermal injections of 10-100 mM stearic acid in olive oil produced mild erythema and slight induration to the skin of guinea pigs and rabbits (Elder, 1987).

Short-Term Toxicity

In 2-wk toxicity studies, F344/N rats were topically treated five times a week with 125 to 2000 mg/kg DEA and B6C3F1 mice were treated with 160 to 2500 mg/kg DEA. Deaths occurred among male rats and male and female mice of the highest dose groups and in female rats of the two highest dose groups. In the higher dose groups of both rats and mice, body weight gains were reduced. Rats had dose-dependent hematologic and renal function changes, ulcerative skin lesions at the site of application (accompanied by inflammatory cell infiltration), hyperkeratosis, and acanthosis (hyperplasia) of the epidermis. Hyperkeratosis, without ulceration, was observed in some of the rats. In mice, ulceration at the site of application and acanthosis, without ulceration or inflammatory cell infiltration, were observed (NTP, 1992).

When 18 mmol% myristic acid and stearic acid were applied to the external ears of rabbits for six weeks, slight irritation was observed with myristic acid and no irritation was observed with stearic acid. Slight local edema was observed among rabbits after 4 wks of topical application of product formulations containing 2.0% stearic acid (Elder, 1987).

A formulation containing 17.0% Stearamide MEA was tested in a 4-wk dermal toxicity study using rabbits. The backs of nine New Zealand albino rabbits were clipped and 2.0 g/kg of a 10% aq. solution of the formulation was applied by gentle inunction five days a week for a total of 20 applications. The treatment sites were abraded on three of the animals, while the skin of the remaining six rabbits was left intact. A control group of rabbits was untreated. Observations for gross signs of dermal irritation and systemic toxicity were made daily, and hematology studies were conducted with blood samples taken 24 h after the first application. All of the animals were killed at the end of the study for necropsy.

No deaths occurred during the study. One of the rabbits had an overall weight loss of 3 g at the end of the study, but the weights of the other rabbits were similar to those of the controls. There were no treatment related clinical signs of toxicity. The only change in blood chemistry parameters occurred with the mean glucose value, which was significantly lower as compared to the concurrent control value. However, the investigators noted that this value was within the historical range for rabbits and was related primarily to low glucose values for two rabbits. Therefore, they considered this alteration to be due to chance randomization. No gross or microscopic lesions were found during necropsy and histopathologic evaluation (CTFA, 1975b).

Subchronic and Chronic Toxicity

Percutaneous application of 4 mg/kg/day MEA to rats resulted in non-specific histological changes in the heart and lungs. Hepatotoxic manifestations included fatty degeneration of the liver parenchyma and subsequent focal necrosis. In another study, no systemic toxicity was observed when a hair dye formulation containing 2.0% DEA was applied to the skin of rabbits for 13 wks (Elder, 1983a).

In 13-wk dermal toxicity studies, rats were treated with 32-500 mg/kg DEA and mice were treated with 80-1250 mg/kg DEA five times a week. Some of the animals from the high dose groups died before the end of the study. Surviving animals in the higher dose groups had reduced body weight gains. In studies with rats, dose-dependent changes in hematology and renal function were observed. Skin lesions, including ulceration and inflammation, hyperkeratosis, and acanthosis, were found at the sites of application. There was an increase in the liver weights of rats, but no associated histopathological changes were found. Demyelination in the brain and spinal cord, and nephropathy, renal tubular necrosis, and/or tubular mineralization were also found. In studies with mice, cytological alterations in the liver and/or hepatocellular necrosis, renal tubular epithelial necrosis, and cardiac myocyte degeneration were observed (NTP, 1992).

In a 13-wk dermal toxicity studies, two cosmetic product formulations containing up to 5% stearic acid produced moderate skin irritation in rats receiving 4.0 ml/kg and 227 mg/kg doses. All other physiological parameters were normal (Elder, 1987).

A formulation containing 5.27% Stearamide MEA was tested in a 13-wk dermal toxicity study using female albino rats (number of animals not stated). Each animal was treated topically with the formulation five days a week. There was no evidence of toxicity during the study, and no treatment related gross or microscopic lesions were found during necropsy and microscopic examination (CTFA, 1982).

Irritation and Sensitization

DEA had little potential for rabbit skin irritation in acute and subchronic skin irritation tests. MEA was corrosive to rabbit skin at a 30% concentration in a single semi-occluded patch application and at concentrations of 10% and greater following 10 open applications over a period of 14 d. No data on sensitization were available on either DEA or MEA. However, in studies of TEA, no sensitization was observed in guinea pigs treated with undiluted TEA (Elder, 1983a).

Undiluted Isostearic acid caused minimal irritation to the skin of rabbits, whereas no irritation was noted when it was diluted to 15% in corn oil. Product formulations containing Isostearic acid produced minimal to moderate skin irritation, most probably by virtue of the

other ingredients present in the formulations (Elder, 1983b).

In single insult occlusive patch tests for primary irritation, commercial grades of stearic acid, at doses of 35-65%, produced no to moderate erythema and slight, if any, edema in the skin of rabbits. Slight increases in irritation were observed in repeated patch tests of myristic acid (Elder, 1987).

In maximization studies with two cosmetic product formulations containing 1.0% stearic acid, slight reactions were observed to challenge patches. These formulations were considered weak, grade I, sensitizers. In another maximization study, after intradermal induction and booster injections of a formulation containing 3.5% stearic acid, reactions to topical challenge applications of the formulation were few and minimal in intensity (Elder, 1987).

A mixture containing 35-40% Stearamide DEA (0.5 g) was applied under occlusive patches to intact and abraded skin of three albino rabbits for 24 h. The sites were scored when the patches were removed and 48 h later. The primary irritation index for this mixture was 0 (Leberco Laboratories, 1971b).

The primary irritation index of a formulation containing 17.0% Stearamide MEA was 1.00/8 for a group of three rabbits (CTFA, 1975c).

Phototoxicity and Photosensitization

No data on phototoxicity were available on DEA or MEA; however, negative results were reported in a study of guinea pigs treated topically with a suntan lotion containing 1% TEA followed by exposure to UVA (Elder, 1983a).

Isostearic acid caused moderate irritation to the skin of rabbits in a phototoxicity study, but there was no statistically significant difference in the scores between the irradiated and the non-irradiated sites (Elder, 1983b).

Skin lotion formulations containing 2.8% stearic acid were not photosensitizing to the skin of guinea pigs (Elder, 1987).

Comedogenicity

A product formulation both with and without 2.5% Isostearic acid was tested in a rabbit ear comedogenicity assay. The formulations without Isostearic acid was irritating but did not produce comedones; however, the formulation with Isostearic acid was both irritating and comedogenic (Elder, 1983b).

Ocular Irritation

DEA and MEA were irritating to the eyes of rabbits at concentrations of 50% and 5%, respectively (Elder, 1983a).

Undiluted Isostearic acid produced no significant ocular irritation in Draize rabbit irritation tests, whereas variable degrees of irritation were produced by product formulations containing Isostearic acid (Elder, 1983b).

Myristic acid and stearic acid alone, as well as cosmetic product formulations containing either 1.5% myristic acid or 1-65% stearic acid produced no to minimal irritation after single and multiple installations into the conjunctival sacs of rabbits. Irritation was primarily in the form of very slight conjunctival erythema (Elder, 1987).

The ocular irritation potential of a mixture containing 35-40% Stearamide DEA was tested using three albino rabbits. The right conjunctival sac of each rabbit was instilled with 0.1 g of the mixture and the left eye served as the control. Examinations of both eyes were conducted every 24 h for 4 days, and then at day 7. No irritation was observed (Leberco Laboratories, 1971c).

No signs of irritation were observed when a formulation containing 5.27% Stearamide MEA was instilled into the conjunctival sacs of six rabbits (CTFA, 1981a), and only minimal irritation was observed with a formulation containing 17.0% Stearamide MEA (CTFA, 1975d).

Moderate eye irritation was observed in Draize tests with formulations containing 8.0% Isostearamide DEA (CTFA, 1983a) and 17.0% Stearamide MEA (CTFA, 1975e).

Ikarashi et al. (1993) reported on cytotoxicity assays which have correlations between in vitro cytotoxicity and the results of in vivo Draize tests. Three different types of cell lines were used in the neutral red assay: Chinese hamster lung fibroblast V79 cells, primary rabbit corneal cells, and normal human epidermal keratinocytes. The cells were incubated with various concentrations of Myristamide DEA for 24 h, followed by incubation with neutral red, and the concentration inducing a 50% reduction in neutral red uptake (IC50) was determined for each cell line. The IC50 values for Myristamide DEA were 15.2 µg/ml for V79 cells, 23.9 µg/ml for rabbit corneal cells, and 6.2 µg/ml for human epidermal keratinocytes. In the Draize test, the DS20 (the concentration predicted to produce a Draize score of 20 (out of a maximum possible score of 110) was 14.5 w/w% Myristamide DEA.

Inhalation Studies

In short-terms studies, 200 ppm DEA vapor and 1400 ppm DEA aerosol caused respiratory difficulties and some deaths in rats. In longer-term studies, increased liver and kidney weights were reported. Continuous exposure to 5-6 ppm MEA vapor caused skin irritation and lethargy in dogs, guinea pigs, and rats. Mortality was observed among dogs exposed to 12-26 ppm MEA vapor and among rodents exposed to 66-75 ppm MEA vapor. Exposure to 66-102 ppm MEA caused behavioral changes and pulmonary and hepatic inflammation, hepatic and renal damage, and hematologic changes in dogs and rodents (Elder, 1983a).

TERATOGENICITY AND REPRODUCTION STUDIES

No evidence of teratogenicity was observed when rats were treated topically with hair dyes containing 2.0% DEA or were fed a composite hair dye and base containing 22% MEA. There were no dose-related significant differences in male and female fertility, or teratogenic effects when up to 7800 ppm of a composite hair dye containing 22% MEA was fed to either male or female rats. When this same composite was administered by gavage to pregnant rabbits during gestation, no teratologic effects were observed (Elder, 1983a).

MUTAGENICITY

The ethanolamines were non-mutagenic in the Ames test and TEA is also non-mutagenic to Bacillus subtilis. TEA did not cause DNA-damage inducible repair in an unscheduled DNA synthesis test (Elder, 1983a).

Stearic acid was inactive in aneuploidy induction tests and in the Ames test (Elder, 1987).

CARCINOGENICITY

There was a higher incidence of malignant lymphoid tumors in female mice fed diets containing TEA for their whole lifespan than in male mice on the same diet or in control mice. However, TEA had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months (Elder, 1983a). DEA is currently under test in an carcinogenesis bioassay being conducted by the National Toxicology Program (NTP, 1994).

No evidence of carcinogenicity was observed in studies of rats fed 3000 ppm stearic acid for 30 wks or 50 g/kg/day stearic acid for 24 wks. In subcutaneous studies, a low incidence of carcinomas, sarcomas, and lymphomas were observed in mice receiving repeated subcutaneous injections of up to 82 mg stearic acid (Elder, 1987).

CLINICAL STUDIES

Dermal Irritation and Sensitization

Clinical skin testing of TEA and cosmetic products containing TEA and DEA resulted in mild skin irritation at concentrations above 5%. There was very little skin sensitization. A dyeless base formulation containing 11.47% MEA and a hair preparation containing 1.6%

DEA and 5.9% MEA were irritating to human skin in patch tests (Elder, 1983a).

In studies of Isostearic acid, no signs of irritation were observed after a 24 h single insult skin patch with undiluted Isostearic acid. Product formulations containing up to 4% Isostearic acid produced, at most, minimal irritation when similarly tested. In another study, there was no evidence that 35% Isostearic acid in mineral oil was an irritant, sensitizer, or photosensitizer. Isostearic acid at 10% in mineral oil was similarly non-irritating and non-sensitizing. Product formulations containing 2.5-2.85% Isostearic acid produced no evidence of contact sensitization when tested in repeated insult patch tests (Elder, 1983b).

Primary and cumulative irritation studies of 100% myristic acid and up to 40% stearic acid in mineral oil were negative. Mild to intense erythema in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies were produced by cosmetic product formulations containing up 8% myristic acid and up to 13% stearic acid. These reactions were generally not related to the fatty acid concentrations in the formulations (Elder, 1987).

In clinical repeated insult patch tests (open, occlusive, and semi-occlusive), maximization tests, and prophetic patch tests with cosmetic product formulations containing up to 13% stearic acid, no primary or cumulative irritation or sensitization was reported. A few subjects reacted to a few, isolated induction patches. Slight, if any, reactions were observed after challenge patching at original or adjacent sites on the upper backs or forearms of some subjects. Intensity of observed reactions to the formulations was not directly related to the concentrations of the fatty acid ingredients (Elder, 1987).

A single insult 24-h patch test of a 1.0% aq. formulation containing 17.0% Stearamide MEA was conducted using 19 subjects. Seven subjects had questionable reactions and three had mild reactions (CTFA, 1981b). In a similar study of a 0.5% formulation containing 8.0% Isostearamide DEA, six of 18 subjects developed a questionable reactions to the formulation and one subject developed a mild reaction (CTFA, 1983b).

The cumulative irritation potential of a formulation containing 5.0% Stearamide MEA was conducted using 14 volunteers. Occlusive patches of 0.2 ml of the formulation were applied to the back of each panelist for 23 h for 21 consecutive days. Test sites were scored 24 h after each application. The composite total score was 156/882. The investigators concluded that this formulation was slightly irritating (Hill Top Research, 1977).

A formulation containing 5.27% Stearamide MEA was tested in a repeated insult patch test using 100 volunteers. The formulation (0.1 ml) was applied under occlusive patches to the backs of each subject for 24 h on Mondays, Wednesdays, and Fridays for 3 wks. After a 2-wk non-treatment period, challenge patches of the formulation were applied to previously untreated sites. One subject had a questionable reaction following the fifth induction patch, but there was no evidence of sensitization in any of the subjects (CTFA, 1981c).

Photosensitization

There was no phototoxicity and photosensitization reactions with products containing up to 20.04% TEA (Elder, 1983a). Cosmetic product formulations containing up to 13% stearic acid produced no photosensitization in human subjects. There were slight reactions to a few induction patches (Elder, 1987).

Inhalation

MEA inhalation by humans has been reported to cause immediate allergic responses of dyspnea and asthma and clinical symptoms of acute liver damage and chronic hepatitis (Elder, 1983a).

SAFETY ASSESSMENT OF OTHER DIETHANOLAMIDES

Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA are fatty acid diethanolamides that were reviewed by the CIR Expert Panel in an earlier safety assessment (Elder, 1986). They are similar to the ingredients reviewed in this report both in their chemistry and use in cosmetics.

In general, these four fatty acid alkanolamides were slightly toxic to non-toxic to rats in formulation and inert vehicles via acute oral administration. Lauramide DEA was the most toxic with an LD50 of 2.7 g/kg. Lauramide DEA was not a significant oral toxin in rats or dogs when administered orally at concentrations of up to 2% of the diet in a subchronic study. Subchronic oral toxicity data were not available for Cocamide DEA, Linoleamide DEA, and Oleamide DEA. However, noting the low toxicity demonstrated by Lauramide DEA and the low acute oral toxicity of all four ingredients, the CIR Expert Panel agreed that the three ingredients were probably not toxic after oral administration. Low toxicity was further supported by the chemical and structural similarities of the four ingredients.

In acute dermal studies, 50% Lauramide DEA and 100% Linoleamide DEA were nontoxic. In various cosmetic formulations, Cocamide DEA, 1.92%, Lauramide DEA, ≤5%, and Linoleamide DEA, 3.0% in a ≤25% solution which was rinsed after 15 min, were not dermal toxins in subchronic animal studies. Oleamide DEA was not tested for dermal toxicity.

Thirty percent Cocamide DEA in propylene glycol was at least a minimal eye irritant and a moderate skin irritant under occlusive conditions using rabbits. Lauramide DEA and Linoleamide DEA in inert vehicles and formulations were mild to moderate eye irritants, mild skin irritants in immersion tests, and mild to severe skin irritants in cumulative and closed patch tests. Undiluted Oleamide DEA was not an eye irritant, but 70% Oleamide DEA was a moderate skin irritant in single and cumulative applications.

Lauramide DEA did not demonstrate mutagenic activity in four separate Ames-type assays using Salmonella typhimurium, one DNA-damage assay using Bacillus subtilis, or two studies on in vitro transformation of hamster embryo cells. Lauramide DEA was mutagenic in an Ames test when assayed at 50 µg in a spot test. No data were available on the mutagenic or carcinogenic activity of Cocamide DEA, Linoleamide DEA, and Oleamide DEA.

Most of the clinical studies on Cocamide DEA, Lauramide DEA, and Linoleamide DEA were conducted with cosmetic soaps and shampoos containing these ingredients. Generally, these products were mild skin irritants but not sensitizers or photosensitizers. Linoleamide DEA, tested full strength, was not an irritant or sensitizer in a repeat insult patch test.

The Panel noted that nitrosamide contamination of these ingredients is possible in one of two ways: either by pre-existing contamination in the diethanolamine used to manufacture the diethanolamide or by nitrosamine formation via the presence of nitrosating agents in formulations containing a diethanolamide. Therefore, they decided that Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA were safe as cosmetic ingredients when free of nitrosamines and not used in cosmetic products containing nitrosating agents.

SUMMARY

Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA are mixtures of the ethanolamides of Isostearic, Myristic and Stearic Acids, respectively, and are used in cosmetics as foam boosting surfactants and as aqueous viscosity increasing agents. Data submitted to CIR reported that Isostearamide DEA, Myristamide DEA, and Stearamide DEA and MEA are used at the following concentrations: in anti-perspirants at 15%, in shampoos at 6%, in shower gels 5%, and in perms and relaxers at 2%.

Stearamide DEA and MEA had little toxicity when tested in acute oral studies at concentrations up to 40%. Longer term studies on these types of mixtures were not available.

However, short-term and subchronic studies of DEA indicate that this component affects the kidneys and livers of rats and mice. In general, it appears that DEA is more toxic than MEA. Thrombosis, aortic atherosclerosis, anorexia, and mortality were observed in feeding studies of stearic acid.

In both short-term and subchronic dermal studies, no evidence of toxicity or irritation was observed with formulations containing Stearamide MEA. MEA alone caused non-specific microscopic lesions in the heart and lungs of rats, as well as hepatic lesions; however, formulation studies of this ingredient were negative. In studies of DEA, effects on the kidneys and livers of mice and rats were observed, as well as skin lesions at the sites of application.

Little dermal irritation was observed in studies of formulations containing Stearamide DEA. However, in studies of component parts, MEA, but not DEA, was corrosive to the skin of rabbits, and Isostearic and stearic acid were minimal to moderate irritants. Also, formulations containing stearic acid had a weak potential for sensitization.

Some ocular irritation was observed in formulation studies of Stearamide DEA and Isostearamide DEA, as well as in studies of the separate ethanolamines and long-chain fatty acids.

Exposure to DEA and MEA in vaporized or aerosolized form caused respiratory difficulties, behavioral changes, skin irritation, hepatic and renal damage, and hematologic effects in animals. Clinical inhalations studies of MEA report immediate allergic responses of dyspnea and asthma and clinical signs of acute hepatic damage and chronic hepatitis.

In reproduction and teratology studies using rats, MEA in the diet had no effect on male and female fertility or on fetal development. No teratogenic effects were observed in pregnant rats following topical exposure to hair dyes containing DEA during gestation, or in pregnant rabbits given a composite hair dye and base containing MEA by gavage.

No mutagenicity or carcinogenicity data specifically on the mixtures of ethanolamides of fatty acids were available. However, the ethanolamines and stearic acid were negative in mutagenicity assays. TEA in the diet increased the incidence of malignant tumors in female mice as compared to male mice on the same diet or in control mice. However, no carcinogenicity or cocarcinogenicity was found in dermal studies. There was no significant evidence of carcinogenicity in oral or subcutaneous studies of stearic acid.

In clinical irritation and sensitization studies, slight irritation but no sensitization was observed with formulations containing Stearamide MEA. Similar results were observed in studies of the ethanolamides and fatty acids alone.

In a earlier review of other diethanolamines, the CIR Expert Panel evaluated the safety of Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA. In general, these ingredients had little oral and dermal toxicity in studies using animals. Mild to moderate dermal and ocular irritation were observed with most of these ingredients. Lauramide DEA was negative in mutagenicity assays, but no mutagenic or carcinogenic data were available on the other ingredients. In clinical studies, these diethanolamines were mild skin irritants but not sensitizers or photosensitizers.

DISCUSSION

The Expert Panel noted the marked absence of safety data specifically on Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA. Since the basic components of these ingredients (DEA, MEA, Isostearic Acid, Myristic Acid, and Stearic Acid) were already evaluated by the Panel in previous reviews, data on the component parts were used as a basis for the assessment of safety of these six ingredients. Additionally, the Expert Panel reviewed data on diethanolamides that were evaluated in an earlier CIR report. Excerpts from earlier Expert Panel discussions of the component ingredients are presented below in italics.

***DEA and MEA**: In regard to DEA, the Panel was concerned about its potential for nitrosation in the presence of N-nitrosating agents, as well as the dermal and ocular irritation potential of this ingredient. MEA was also both a dermal and ocular irritant in animal studies, and clinical studies with formulations containing MEA indicated that it is a human skin irritant. The longer MEA was in contact with the skin, the greater the likelihood of irritation. With these issues in mind, the Panel concluded that DEA and MEA were safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. MEA should be used only in rinse-off products, and the concentration of DEA should not exceed 5% in products intended for prolonged contact with the skin. DEA should not be used in products containing N-nitrosating agents.*

***Isostearic Acid**: The Panel expressed concern regarding the production of comedones in the rabbit ear assay by a product formulation containing commercially available Isostearic Acid. The Panel recognized that the available tests were inadequate to predict the potential for human comedogenicity of an ingredient used in a product formulation. However, it was considered a potential health effect that should be considered when Isostearic Acid is used in cosmetic formulations. The Panel concluded that Isostearic Acid was safe as a cosmetic ingredient.*

***Myristic and Stearic Acid**: The Panel noted the lack of safety data, specifically on Myristic Acid. However, due to Myristic Acid's structural similarity to Stearic Acid, as well as to oleic, lauric, and palmitic acid (which were reviewed in the same report), the Panel felt that the conclusions reached for the other ingredients could be extrapolated to myristic acid. The Panel concluded that both Myristic and Stearic Acid were safe for use in cosmetics.*

***Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA**: The Expert Panel recognized that the only data on subchronic oral toxicity was on Lauramide DEA. However, noting the low toxicity demonstrated by this ingredient and the low acute oral toxicity of all four ingredients, they decided that Cocamide DEA, Linoleamide DEA, and Oleamide DEA were probably not significantly toxic after oral administration. The chemical and structural similarities of the four ingredients further support this view.*

However, nitrosamine contamination of diethanolamine and fatty acid diethanolamides and nitrosamine formation in formulations were considered potential problems in using these ingredients. Thus, the Expert Panel concluded that Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA are safe as cosmetic ingredients, but should not be used in cosmetic products containing nitrosating agents.

Because these ethanolamine-fatty acid esters may be hydrolyzed to the free ethanolamine and fatty acid, principal concerns were the ability of MEA and DEA to cause irritation and the potential for nitrosation in the presence of N-nitrosating agents. The release of Stearic Acid, Myristic Acid, and Isostearic Acid as a result of hydrolysis of the parent ingredients were considered to present a lesser cause for concern. In general the Panel believed that restrictions to address the concerns about free ethanolamines should be continued, specifically because MEA and DEA could be produced from the esters by hydrolysis.

Even in the event of complete hydrolysis of the ethanolamine-fatty acid ester present in a formulation at "x"%, however, it is expected that no more than 0.33"x"% of free DEA or 0.22"x"% of free MEA would be released. Given that use concentrations are expected to be only up to 10% for the DEA-fatty acid esters and 25% for the MEA-fatty acid esters, and that partial hydrolysis is more likely to occur, the yield of free ethanolamine is not likely to be greater than 5% in a formulation, which is the concentration limit previously recommended by this Panel for free amines.

The Panel noted its earlier conclusion that MEA should be used only in rinse-off products. There were data available in this report on irritation produced by Stearamide MEA suggesting it to be less irritating than Stearic Acid or MEA alone; in addition, it was not sensitizing. The likelihood is that these data are relevant to the other MEA containing ingredients as well. Therefore, the Expert Panel concluded that there was no need

to restrict the MEA-fatty acid esters to rinse-off products. The ethanolamines are clearly irritants and can easily be produced from these esters by hydrolysis. However, the Expert Panel believed a 5% concentration limitation is still appropriate.

The Expert Panel also recognized that these ingredients were only tested up to a concentration of 40% for the DEA-fatty acids and 17% for the MEA-fatty acids. For that reason the Panel believes these concentrations to represent the highest concentrations for which it can be certain these ethanolamine-fatty acid esters can be used safely.

Combining all of these concerns, and recognizing that rinse-off use presented little concern, the Expert Panel arrived at a maximum concentrations for both the ethanolamine-fatty acid esters and for release of free ethanolamines when these esters are used in cosmetic formulations.

CONCLUSION

Based upon the data included in this report and those data summarized from previous CIR reports, the Expert Panel concludes that Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA are safe for use in rinse-off products. In leave-on products, these ingredients are safe for use at concentrations that will limit the release of free ethanolamines to 5%, but with a maximum use concentration of 17% for Isostearamide, Myristamide, and Stearamide MEA and of 40% for Isostearamide, Myristamide, and Stearamide DEA. These ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

ACKNOWLEDGEMENT

Susan Pang, Scientific Analyst and Writer, prepared this report.

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JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 12, Number 3, 1993
Mary Ann Liebert, Inc., Publishers

Final Report on the Safety Assessment of Acetamide MEA

ABSTRACT

Acetamide MEA is used in cosmetics as a skin conditioning agent-humectant and hair conditioning agent. Oral LD_{50}'s of 27 g/kg were reported for Acetamide MEA in rats. No rabbits died following an acute dermal exposure of 20 ml/kg Acetamide MEA. In ocular irritation studies, 70% Acetamide MEA and cosmetic formulations containing 1.3% Acetamide MEA were classified as nonocular irritants in rabbits. Only mild skin irritation occurred following a 24-h skin exposure to undiluted Acetamide MEA. In the maximization test, Acetamide MEA was classified as a nonsensitizer in guinea pigs when tested at a concentration of 5.0%. Neither primary irritation nor sensitization reactions to 7.5% Acetamide MEA were observed in a human repeated insult patch test. Acetamide MEA was not nonmutagenic in the Ames assay. In the presence of nitrosating agents, Acetamide MEA may form N-nitroso compounds; acetamide may be a minor impurity in Acetamide MEA. On the basis of the data presented in this report, it is concluded that Acetamide MEA is safe as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products and is safe in the present practice of use in rinse-off products. Cosmetic formulations containing Acetamide MEA should not contain nitrosating agents or significant amounts of free acetamide.

INTRODUCTION

ACETAMIDE MEA IS AN aliphatic amide used in cosmetic formulations as a skin conditioning agent-humectant and hair conditioning agent. It may be produced by the acetylation of ethanolamine, followed by vacuum distillation.

CHEMISTRY

Chemical and Physical Properties

Acetamide MEA (CAS no. 142-26-7) is the aliphatic amide that conforms to the formula (Estrin et al., 1982a):

$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}-NH-CH_2CH_2OH$$

Other names for this chemical are Acetamide, N-(2-Hydroxyethyl)-; N-beta-Hydroxyethylacetamide; N-(2-Hydroxyethyl)Acetamide; beta-Hydroxyethylacetamide; 2-Acetamidoethanol; 2-Acetylaminoethanol; Acetylcolamine, N-Ethanolacetamide; N-Acetyl Ethanolamine; and Hydroxyethyl Acetamide (RTECS, 1988). Acetamide MEA is usually marketed as a 70–75% aqueous solution (Hunting, 1983). It is said to be compatible with all types of surfactants (Hunting, 1983) and is soluble in alcohol, ether, acetone, and water (Hawley, 1971; Weast and Astle, 1982). Additional properties of Acetamide MEA are listed in Table 1.

The formation of carcinogenic N-nitrosamines (e.g., N-nitrosopiperidine) from dissolved NOCl gas in aqueous 0.1 M NaOH solution was evaluated in the presence of the following alkanolamines: triethanolamine, diethanolamine, N-methylethanolamine, N,N-diethylethanolamine, N-nitrosodiethanolamine, N-methyl-N-nitrosoethanolamine, choline chloride, and N-acetylethanolamine (Acetamide MEA). An appropriate secondary amine was added after all of the nitrosyl gas had reacted with either the alkanolamine or the solvent. In the absence of alkanolamines, along with an approximately 6-fold excess of NOCl, close to 35% of the amine was converted to N-nitrosamine in less than 3 min. However, in the presence of alkanolamines, the reactions were slower and often more extensive. It has been suggested that alkanolamines increase the extent of the reaction by initial formation of an alkyl nitrite derivative, which then reacts with the secondary amine to yield an N-nitroso product (Challis and Shuker, 1980).

METHODS OF PRODUCTION

Acetamide MEA is prepared by the reaction of acetic acid with monoethanolamine (CTFA, no date). Additional methods of production that have been reported involve

Table 1. Properties of Acetamide MEA

Form	Clear liquid	Scher Chemicals, Inc., 1977
Molecular weight	103.12	Weast and Astle, 1982
Activity	70% minimum	Scher Chemicals, Inc., 1977
Diluent (water)	30.0% maximum	Scher Chemicals, Inc., 1977
Ionic nature	Nonionic	Scher Chemicals, Inc., 1977
Shelf life	1 year minimum in closed container	Scher Chemicals, Inc., 1977
Density	1.1079 (25/4°C)	Weast and Astle, 1982
Specific gravity	1.12 ± 0.05 (25°C)	Scher Chemicals, Inc., 1977
	1.122 (20/20°C)	Hawley, 1971
Refractive index	1.4674 (20°C)	Weast and Astle, 1982
	1.4380 ± 0.001 (25°C)	Scher Chemicals, Inc., 1977
Solubility	Soluble in most alcohols, glycols, diols, triols, polyols glycol ethers, water, and acetone	Scher Chemicals, Inc., 1977; Weast and Astle, 1982
Boiling point	151°C	Sax, 1979
Melting point	63.5°C	Weast and Astle, 1982
Freezing point	15.8°C	Sax, 1979
Flash point (Anhydrous)		
Open cup	over 180°C	Scher Chemicals, Inc., 1977
Closed cup	over 100°C	
Autoignition temperature (°F)	860°F	Sax, 1979

acetamide and ethylene oxide, monoethanolamine and acetyl chloride (CTFA, no date), and the acetylation of ethanolamine using acetic anhydride, followed by vacuum distillation (Heyns and Bebenburg, 1955).

ANALYTICAL METHODS

Acetamide MEA has been identified via the following methods: thin layer chromatography (Chrystal et al., 1980), high performance liquid chromatography (Scher Chemicals, Inc., 1979; Clairol, Inc., 1991), and gas chromatography (GC) (CTFA, no date).

IMPURITIES

An analysis of four typical production lots of Acetamide MEA by gas chromatography (with flame ionization detection [FID] detection) indicated the presence of MEA and acetamide. The results were as follows: Lot 7707 (0.43% w/w MEA), Lot 7579 (0.79% w/w MEA and 0.030% w/w acetamide), Lot 7618 (0.48% w/w MEA and 0.065% w/w acetamide), and Lot 7617 (0.55% w/w MEA) (CTFA, no date). Different concentrations of MEA and acetamide impurities were reported in a second analysis in which the same four lots of acetamide MEA were analyzed by GC-mass spectrometry (MS): Lot 7707 (0.0027% w/w MEA and 0.0028% w/w acetamide), Lot 7579 (0.0006% w/w MEA and 0.0006% w/w acetamide), Lot 7618 (0.0029% w/w MEA and 0.0030% w/w acetamide) and Lot 7617 (0.0017% w/w MEA and 0.0020% w/w acetamide) (Clairol, 1992). The investigators stated that the results of the GC-MS analysis invalidate the GC-FID analysis, because, with the former method, an unknown coeluting peak was detected. Thus, concentrations of impurities reported in the second analysis are much lower than those in the first analysis.

Acetamide, one of the impurities mentioned in the preceding paragraph, induced hepatocellular carcinomas when administered orally to male and female rats (Fleischman et al., 1980; Flaks et al., 1983) and malignant lymphomas when administered orally to male and female mice (Flaks et al., 1980).

A commercial preparation of Acetamide MEA, representing an aqueous solution of active material, was analyzed by high-performance liquid chromatography. In this analysis, Acetamide MEA represented 80.55% of the total peak area and 3 other components represented 8.72%, 8.57%, and 1.76% of the peak area, respectively. The authors stated that none of these components represented free acetamide or monoethanolamine, and that there was no further determination of their identity (Clairol, Inc., 1991).

Acetamide MEA was analyzed for N-nitrosodiethanolamine content via high performance liquid chromatography (detector = TEATH Model 502 Analyzer). N-nitrosodiethanolamine was not detected (limit of detection = 0.05 ppm) (Scher Chemicals, Inc., 1979).

USE

Cosmetic

Acetamide MEA is used as a skin conditioning agent-humectant and hair conditioning agent in cosmetic products (Nikitakis, 1988).

The product formulation data submitted to the Food and Drug Administration (FDA) for Acetamide MEA indicated that it was contained a total of 102 cosmetic product formulations (FDA, 1992). Acetamide MEA was used in the following products: bubble baths; other bath preparations; hair conditioners; hair shampoos (noncoloring); tonics, dressings, and other hair grooming aids; wave sets, other hair preparations (noncoloring); and moisturizing skin care preparations. The greatest reported use of Acetamide MEA was in hair conditioners.

Concentration of use values are no longer reported to the FDA by the cosmetics industry (Federal Register, 1992). However, 1989 product formulation data submitted to FDA indicated that Acetamide MEA was used at concentrations up to 25% (FDA, 1989).

Product formulation data on Acetamide MEA are included in Table 2.

Cosmetic products containing Acetamide MEA are applied to the hair and skin and may come in contact with ocular and nasal mucosae.

Product formulations containing Acetamide MEA may be used daily or on a monthly basis. Many of the products may be expected to remain in contact with body surfaces for as briefly as a few minutes to as long as a month. Each product has the potential for being applied many times over a period of several years.

International

Acetamide MEA appears in the list of cosmetic ingredients approved for use in cosmetic formulations marketed in Japan (Nikko Chemicals Co., Ltd., 1992). This ingredient does not appear in the list of ingredients prohibited from use in products marketed in the European Economic Community (EEC Cosmetics Directive, 1990).

Noncosmetic

Acetamide MEA has the following noncosmetic uses: detoxifier (Hunting, 1983); plasticizer for polyvinyl alcohol and for cellulosic and proteinaceous materials; humectant for paper products, glues, cork, and inks; high boiling solvent for fountain-

Table 2. Product Formulation Data on Acetamide MEA (FDA, 1992)[a]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*Maximum concentration of use (%) (FDA, 1989)*
Other bath preparations	132	3	Category not reported in 1989
Hair conditioners	478	60	25
Hair shampoos (noncoloring)	909	14	5
Tonics, dressings, and other hair grooming aids	290	12	10
Wave sets	180	7	5
Other hair preparations (noncoloring)	177	3	Category not reported in 1989
Moisturizing skin care preparations	747	3	Category not reported in 1989
1992 totals		**102**	

[a]CIR requests that the cosmetics industry provide current formulation data on each product category.

pen inks; and textile conditioner (Hawley, 1971). Adhesives containing Acetamide MEA may be used safely as components of articles intended for use in packaging, transporting, or holding food (21CFR:175.105).

TOXICOLOGY

Acute Oral Toxicity

An LD_{50} of 27.66 g/kg was reported for Acetamide MEA in a study involving rats (Deichmann, 1969).

In another study, the acute oral toxicity of Acetamide MEA (activity = 70% minimum; specific gravity = 1.12) was evaluated using 6 groups of 6 albino rats (three males, three females per group; weights = 206–298 g). The following oral dosages (one per group) were administered: 5.0, 25.0, 26.5, 27.3, 28.0, and 31.5 g/kg. The animals were observed for pharmacologic activity and drug toxicity at 1, 3, 6, and 24 h postadministration and, subsequently, daily for a total of 14 days. Necropsy was performed on surviving animals as well as those killed at the end of the observation period. The LD_{50} was 26.95 (25.55–28.43) g/kg (Consumer Product Testing Company, Inc., 1981a).

The acute oral toxicity of a liquid hair product (bulk density = 1.01 g/ml) and a foam hair product, both containing 1.3% Acetamide MEA, was evaluated using young adult male and female Sprague-Dawley strain rats (weights = 193–271 g). All animals were fasted 18–20 h prior to dosing. Three dosages (10.0, 13.0, and 16.9 g/kg) of the liquid product were administered via gavage to 3 pairs of rats (1 male, 1 female), respectively. The foam product was administered to 3 male rats and 3 female rats at a dosage of 25 ml/kg. All animals were observed at 0.5, 2, and 4 h postadministration and, subsequently, daily for 7 days. At the conclusion of the study, the animals were killed and necropsy was performed. None of the rats dosed with either the liquid or foam product died. No visible lesions were found in any of the three pairs of rats dosed with the liquid product. The necropsy results for animals dosed with the foam product were not included (Hazleton Laboratories America, Inc., 1985).

Acute Dermal Toxicity

The acute dermal toxicity of Acetamide MEA was evaluated using six rabbits (weights and strain not stated). None of the animals dosed with 20 ml/kg of the test substance died (Deichmann, 1969).

Subchronic Dermal Toxicity

The subchronic percutaneous toxicity of a hair product (foam) containing 1.3% Acetamide MEA was evaluated using 10 male (weights = 2112–2971 g) and 10 female (weights = 2133–3010 g) New Zealand White albino rabbits approximately 4 months old. Half of the animals, five of each gender, were treated with deionized water (negative control). The product was diluted with deionized water to a concentration of 50.0% w/v (effective concentration of Acetamide MEA = 0.65%) and administered at a constant dosage of 2.0 ml/kg. A glass rod was used to distribute the test solution evenly over the application site, defined as an area between the shoulders and rump (12–15 cm

wide) that had been clipped free of hair. Each animal wore a plastic restraint collar during the 7 h exposure period, after which the collar was removed and the test site washed with tap water and dried. This procedure was repeated once daily (5 days per week) for 13 weeks (91 days). At the conclusion of the study, necropsy was performed on each animal. None of the animals died during the study, and there was no evidence of test substance-related systemic toxicity. Irritation reactions observed at application sites were limited to slight to moderate erythema. These reactions were initially observed on days 44–45, and continued sporadically in 1–4 animals through day 84. No signs of irritation were observed at the application sites of rabbits in the negative control group. There were no test-substance related gross lesions in organs or tissues other than skin at the application site (International Research and Development Corporation, 1987).

Ocular Irritation

The ocular irritation potential of Acetamide MEA (activity = 70% minimum; pH 7.1) was evaluated using six New Zealand White rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of each animal; eyes were not rinsed. The contralateral eye served as the control. Each animal was observed for signs of corneal opacity, iritis, and conjunctivitis at 24, 48, and 72 h postinstillation. If irritation reactions persisted, observations were also made at 4 and 7 days postinstillation. Reactions were scored according to the Draize scale: 0–110. At 24 h postinstillation, a Draize score of 0.7 was reported. Reactions were not observed after 24 h. Acetamide MEA was practically nonirritating to the eyes of rabbits (Consumer Product Testing Company, Inc., 1981b).

The ocular irritation potential of two hair products (liquid and foam) containing 1.3% Acetamide MEA was evaluated using two groups (one product per group) of six young adult, New Zealand white rabbits. The test substance (10 μl, undiluted) was placed on the cornea of one eye of each rabbit via a 100 μl glass syringe; eyes were not rinsed. The contralateral eye served as the control. Ocular reactions were scored on day 1 according to the Draize (1959) scale. Scoring was discontinued after day 1 because no ocular irritation reactions had been observed. Neither the liquid product nor the foam product was classified as an ocular irritant (Hazleton Laboratories America, Inc., 1986).

Skin Irritation

The skin irritation potential of Acetamide MEA was evaluated according to a modification of the procedure by Draize et al. (1944) using 12 albino rabbits. The test substance (500 mg) was applied to the trunk of each animal; patches (open) remained in place for 24 h. The application sites of six rabbits were abraded, whereas those of the remaining rabbits remained intact. The animals were immobilized during the exposure period. At 24 h postapplication, reactions were scored according to the scale of 1 (very slight erythema) to 4 (severe erythema to slight eschar formation); 1 (very slight edema) to 4 (severe edema, raised more than 1 mm and extending beyond the area of exposure). Reactions were also scored at 72 h postapplication. Scores determined at 24 and 72 h were averaged. Well-defined erythema and slight edema were observed. Acetamide MEA was classified as a mild skin irritant (Union Carbide Data Sheet, 1967).

In another study, the skin irritation potential of Acetamide MEA (activity = 70% minimum; pH 7.1) was evaluated using six New Zealand White rabbits. The test

substance (0.5 ml) was applied to two sites, one abraded and one intact. Each site was covered with an occlusive patch for 24 h and then scored for erythema and edema at 24 and 72 h postapplication. The mean irritation scores determined at 24 and 72 h were averaged, and a primary irritation index (PII) was calculated. Acetamide MEA was not a primary skin irritant (PII = 0.43) (Consumer Product Testing Company, Inc., 1981c).

Skin Sensitization

The sensitization potential of Acetamide MEA was evaluated in the modified Magnusson-Kligman maximization test (Magnusson and Kligman, 1969) using 10 female Dunkin-Hartley guinea pigs. During induction, the animals were injected intradermally with 5.0% Acetamide MEA in propylene glycol and 5.0% Acetamide MEA in Freund's adjuvant, and also received a topical application of 100.0% Acetamide MEA (topical induction booster). Prior to induction, the induction sites were pretreated with 5.0% w/w sodium lauryl sulfate in petrolatum. Each animal in the experimental group was challenged with topical wrappings containing Acetamide MEA at concentrations of 50.0% (applied to anterior site) and 100.0% (applied to posterior site) in propylene glycol, respectively. Similarly, the 5 guinea pigs in the control group were each challenged with 50.0% and 100.0% propylene glycol. Challenge reactions were evaluated at 48 and 72 h according to the scale of 0 (no evidence of any effect) to 4 (severe = deep red erythema with or without edema). No positive reactions were observed in the experimental or control group, and the test substance was classified as a nonsensitizer (CTFA, 1988).

MUTAGENICITY

The mutagenicity of Acetamide MEA was evaluated in the Ames test (Maron and Ames, 1983) using strains TA98, TA100, TA1535, TA1537, and TA1538 of *Salmonella typhimurium*. Each strain was incubated for approximately 46–72 h, with Acetamide MEA concentrations ranging from 100 to 5,000 μg/plate both with and without metabolic activation. Negative control cultures (all strains, with and without metabolic activation) were incubated with sterile deionized water (100 μl/plate). Positive control cultures were treated as follows: sodium azide (1 μg/plate: TA100 and TA1535 without activation); 2-aminoanthracene (0.5 μg/plate; all strains with activation); and 4-nitro-o-phenylenediamine (5 μg/plate: TA98, TA1537, and TA1538 without activation). Within the range of concentrations tested, Acetamide MEA was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. These results indicate that Acetamide MEA did not induce base-pair substitution or frameshift mutations in this bacterial test system. The increase in the mean number of revertants in positive control cultures over that noted for the concurrent negative control value for each respective strain was greater than threefold (Clairol Inc., 1991).

The genotoxicity of Acetamide MEA in primary rat hepatocytes was evaluated using the unscheduled DNA synthesis (UDS) assay (Williams 1977, 1980; Butterworth et al., 1987). Rat hepatocyte cultures were exposed to Acetamide MEA concentrations ranging from 5000 to 0.500 μg/ml (solvent = sterile deionized water) in the presence of 10 μCi/ml ^{3}HTdR (47 Ci/mM) for 18.8 h. Positive control cultures were exposed to 4.48×10^{-7} M 2-acetylaminofluorene (0.10 μg/ml) in dimethyl sulfoxide (DMSO) and, negative control cultures, to 10% sterile deionized water. The cells were

examined microscopically and UDS was measured by counting nuclear grains and subtracting the average number of grains in three nuclear-sized areas adjacent to each nucleus (referred to as net nuclear grain count). The net nuclear grain count was determined for at least 50 randomly selected cells per coverslip; nuclei with normal morphology were scored. The criteria for activity in the UDS assay were an increase in the mean net nuclear grain count to at least five grains per nucleus above the concurrent solvent control value and/or an increase in the percentage of nuclei having five or more net grains, such that the percentage of these nuclei in test cultures is at least 10% above the percentage observed in the solvent control cultures. At a concentration of 5,000 μg/ml Acetamide MEA, a slight increase in nuclear labeling was suspected. However, this observation was not confirmed. Acetamide MEA did not induce unscheduled DNA synthesis within the range of concentrations tested, and, therefore, did not induce DNA damage. The positive control, 2-acetyl-aminofluorene was active in the UDS assay (Hazleton Washington, Inc., 1991).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

A facial use test involving 19 female subjects, selected at random, was used to evaluate the skin irritation potential of a product containing 0.5% Acetamide MEA. Each subject was instructed not to wear facial makeup or a moisturizer, and also was examined for any pre-existing condition (erythema, swelling, or dryness) prior to application. The product being tested (0.1 cc) and a control product (0.1 cc) of unknown composition were rubbed onto one side of the face twice daily (6 h interval) for 5 consecutive days. After application, subjects were allowed to apply facial makeup. The following reactions to the test product were observed in a total of three subjects. On the second day of the test, one subject withdrew after observing a reaction, blotchy erythematous plaques in the cheek area, on both sides of the face. Reactions were not observed on the following morning. Another subject withdrew because of reactions classified as moderate erythema and a patchy vesicular response. These reactions were thought to have resulted from contact with poison ivy during the weekend prior to the test. Subsequent follow-up testing in which test and control products were applied to the flex area three times per day for one week revealed no reactions. Minimal erythema and dryness were observed in the third subject. These reactions were collectively referred to as a slight increase over the initial test condition and, more than likely, represented normal fluctuations. The product containing 0.5% Acetamide MEA did not evoke unacceptable clinical irritation, and was comparable to the control product (CTFA, 1987).

Skin Irritation and Sensitization

The skin irritation and sensitization potentials of Acetamide MEA (7.5% w/v in distilled water) were evaluated using 50 subjects. The test substance was applied via an occlusive patch (same site) on Monday, Tuesday, Wednesday, and Thursday for 3 consecutive weeks. Each patch remained in place for 24 h. After patch removal, sites were scored according to the following scale: 0 (no visible erythema) to 4 (severe irritation, consisting of erythema, swelling, papules, and necrosis and extension

beyond the boundaries of contact). The test site was to have been changed only if substantial irritation resulted. Substantial irritation was defined as a score of greater than 1 (erythema). After a nontreatment period of approximately 2 weeks, an occlusive challenge patch was applied for 24 h to a new test site. Reactions were scored immediately after patch removal and 24, 48, and 72 h later. Irritation reactions were not observed during the first week of induction. During the second week, erythema was observed in one subject. During the third week of induction, skin irritation was observed in two subjects. Erythema and swelling were observed in one of the subjects, necessitating a change in the application site; erythema was observed in the other subject. Reactions were not observed during the challenge phase. The authors concluded that the irritation reactions observed were indicative of skin fatigue, and that the test substance did not cause primary irritation or sensitization (Habitant Trading Corporation, 1977).

Skin Sensitization

The skin sensitization potential of a hair product (liquid) containing 1.3% Acetamide MEA was evaluated using 124 subjects (67 males, 57 females; 20–81 years old). The product was diluted with water to a concentration of 50.0% w/v (effective concentration of Acetamide MEA = 0.65%). A total of 111 subjects completed the study; 45 subjects had allergies. The 13 subjects who withdrew did so for reasons unrelated to the conduct of the study. Prior to application of the first induction patch, the test site was wiped with a gauze pad saturated with 95% ethanol or isopropanol. The test substance (0.5 ml) was then applied to the lateral surface of the upper arm, between the shoulder and elbow, via an occlusive patch secured with surgical tape. Patches were applied on Mondays, Wednesdays, and Fridays for a total of nine 24 h induction applications, and the subjects were instructed to clean the test site after each patch removal. Reactions on Monday and Wednesday were scroed at 48 h postapplication according to the scale: 0 (no visible reaction) to 5 (bullous reaction); reactions on Friday were scored at 72 h. After a 17-day nontreatment period, 2 challenge patches (1 at original site and 1 at similar site on opposite arm) were applied for 24 h. Each challenge site was wiped with a gauze pad saturated with 95% ethanol or isopropanol prior to patch application. Reactions were scored at 48 and 96 h postapplication. Twelve subjects had reactions only during the induction phase (mild erythema in 11 subjects, mild erythema with papules and/or edema in 1 subject). Reactions during induction and challenge phases were observed in two subjects. One of these subjects had mild erythema during induction and the first challenge (original and alternate sites), and the other had mild erythema during induction, the first challenge (original and alternate sites), and the second challenge (adjacent site). The authors concluded that there was no evidence of sensitization in any of the subjects tested (Harris Laboratories, Inc., 1986).

SUMMARY

Acetamide MEA (CAS No. 142-26-7) is an aliphatic amide that may be produced via acetylation of ethanolamine using acetic anhydride; the reaction is followed by vacuum distillation. It is usually marketed as a 70.0–75.0% aqueous solution.

N-nitrosodiethanolamine was not detected when Acetamide MEA was analyzed via high-performance liquid chromatography. Both acetamide (up to 0.0030%) and monoethanolamine (up to 0.0029%) were detected when Acetamide MEA was analyzed via gas chromatography–mass spectrometry.

Acetamide MEA is used as a skin conditioning agent-humectant and hair conditioning agent in cosmetic products. Product formulation data reported to FDA in 1989 indicated that this ingredient was used at concentrations up to 25%; concentration of use data are no longer reported to FDA. Current FDA data indicate that Acetamide MEA is used in 102 cosmetic products.

Noncosmetic uses of Acetamide MEA are as follows: detoxifier, plasticizer, humectant for paper products, solvent for fountain-pen inks, and textile conditioner. Adhesives containing Acetamide MEA may be used safely as components of articles intended for use in packaging, transporting, or holding food.

Oral LD50's of 27.66 g/kg and 26.95 g/kg (relatively harmless) were reported for Acetamide MEA in 2 studies involving rats. In another study involving rats, 2 hair products containing 1.3% Acetamide MEA did not cause death at a dosage of 16.9 g/kg, the highest dose tested.

The acute dermal toxicity of Acetamide MEA was evaluated using six rabbits. None of the animals dosed with 20 ml/kg of the test substance died.

The subchronic percutaneous toxicity of a hair product diluted to a concentration of 0.65% Acetamide MEA was evaluated using rabbits. None of the animals died during the study, and no evidence of systemic toxicity was observed.

In ocular irritation studies, Acetamide MEA (activity = 70% minimum) and two hair products containing 1.3% Acetamide were not classified as ocular irritants when instilled (0.1 ml) into the conjunctival sac of the eyes of New Zealand white rabbits.

Mild skin irritation reactions were observed in albino rabbits after Acetamide MEA (500 mg, open patch) was applied to the skin for 24 h. In another study, Acetamide MEA (activity = 70% minimum) was not a skin irritant when applied (0.5 ml, occlusive patch) for 24 h to abraded and intact skin of New Zealand white rabbits.

In the maximization test, Acetamide MEA was classified as a nonsensitizer in guinea pigs when tested at a concentration of 5.0% during induction and at concentrations of 50.0% and 100.0% during the challenge phase.

Acetamide MEA did not induce base-pair substitution or frameshift mutations in the Ames test. Results were also negative in the unscheduled DNA synthesis assay involving rat hepatocytes.

In a 5-day facial use test involving female subjects, a product containing 0.5% Acetamide MEA did not evoke unacceptable clinical skin irritation.

Neither primary irritation nor sensitization reactions to Acetamide MEA (7.5% w/v in distilled water) were observed in a repeated insult patch test (occlusive patches) involving male and female subjects. In another repeated insult patch test (occlusive patches) involving male and female subjects, there were no sensitization reactions to a hair product diluted to 0.65% Acetamide MEA.

DISCUSSION

Concentration of use data are no longer submitted to FDA by the cosmetics industry. Due to this fact, the Expert Panel can no longer make the conclusion "Safe as used," as was previously done, but must now make a conclusion based on the product

and test concentrations used in the report. The results of a human skin sensitization study cited in this report indicate that Acetamide MEA was not a sensitizer at a concentration of 7.5%. This maximum test concentration is the basis for the Panel's conclusion relative to use concentrations of Acetamide MEA in leave-on cosmetic products.

The Expert Panel recognizes that Acetamide MEA may form N-nitroso compounds in the presence of nitrosating agents, and that acetamide may be a minor impurity in Acetamide MEA. In commercial lots of Acetamide MEA, acetamide has been detected at concentrations up to 0.0030%. For formulated cosmetics, the expected breakdown products of Acetamide MEA are acetic acid and monoethanolamine. This means that acetamide in the formulation results from contamination of the starting material and is not a degradation product of Acetamide MEA. Therefore, when used as a cosmetic ingredient, Acetamide MEA should be free of nitrosamines and acetamide, and the finished cosmetic product should not contain nitrosating agents.

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concludes that Acetamide MEA is safe as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products and is safe in the present practices of use in rinse-off products. Cosmetic formulations containing Acetamide MEA should not contain nitrosating agents or significant amounts of free acetamide.

ACKNOWLEDGMENT

The scientific literature review and technical analysis were prepared by Wilbur Johnson, Jr., Senior Scientific Analyst and Writer.

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[1]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, N.W., Suite 310, Washington, DC 20036.

Final Report on the Safety Assessment of Cocamide MEA[1]

Cocamide MEA is a mixture of ethanolamines of fatty acids derived from coconut oil. This cosmetic ingredient functions as a surfactant—foam booster and an aqueous viscosity-increasing agent. To supplement the available data on Cocamide MEA, data from previous safety assessments of Coconut Oil and its derivatives, Monoethanolamine (MEA), and Cocamide DEA (Diethanolamine) were included in this safety assessment. These data suggest little acute, short-term, or chronic toxicity associated with dermal application. MEA vapor, however, is highly toxic. Although DEA is readily nitrosated to form *N*-nitrosodiethanolamine, a known animal carcinogen, MEA has not been found to form a stable nitrosamine. Dermal application of Cocamide MEA at concentrations of 50% was nonirritating to mildly irritating in animal tests. For comparison, Cocamide DEA at a concentration of 30% was a moderate irritant; Coconut Oil was nonsensitizing; and MEA was irritating and corrosive. Cocamide MEA was negative in the Ames Test. Cocamide DEA was positive in some mutagenesis assays, but negative in others. In clinical tests, Cocamide MEA at a concentration of 50% was not irritating in a single-insult patch test. Cocamide DEA at 2% in formulation caused irritation, but not sensitization. Predictive patch tests with a surfactant containing Cocamide DEA at 10% produced no adverse effects. Inhalation of MEA by humans is toxic. Based on the limited data available data on Cocamide MEA, and on the data on those ingredients previously reviewed, particularly Cocamide DEA, it was concluded that Cocamide MEA is safe as used in rinse-off products and safe at concentrations up to 10% in leave-on products. It was further concluded, however, that Cocamide MEA should not be used as an ingredient in cosmetic products in which *N*-nitroso compounds are formed or in formulations that will be aerosolized.

Cocamide Monoethanolamine (MEA) functions as a surfactant—foam booster and aqueous viscosity-increasing agent—in cosmetic formulations. Safety assessments on Cocamide Diethanolamine (DEA), Stearamide MEA, Isostearamide MEA, Myristamide MEA, Coconut Oil and its derivatives, and MEA have been previously evaluated by the Cosmetic Ingredient Review (CIR) Expert Panel. Information from those safety assessments has been included in this report (*in italics*). The following conclusions were made:

Cocamide DEA is safe as used in rinse-off products and safe at concentrations up to 10% in leave-on cosmetic products. Cocamide DEA should not be used as an ingredient in cosmetic products in which *N*-nitroso compounds are formed (Andersen 1996).

Coconut Acid, Coconut Oil, Hydrogenated Coconut Acid, and Hydrogenated Coconut Oil are safe for use as cosmetic ingredients (Elder 1986a).

MEA is safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing of the skin. In products intended for prolonged contact with the skin, the concentration of ethanolamines should not exceed 5 percent. MEA should only be used in "rinse-off" products (Elder 1983).

Stearamide DEA and MEA, Isostearamide DEA and MEA, and Myristamide DEA and MEA are safe for use in rinse-off products; safe for use in leave-on products at concentrations that will limit the release of free ethanolamines to 5%, but with a maximum use concentration of 17% for the MEA forms and 40% for the DEA forms; and none should be used in cosmetic products in which *N*-nitroso compounds may be formed (Cosmetic Ingredient Review [CIR] 1995).

CHEMISTRY

Definition and Structure

Cocamide MEA (CAS No. 68140-00-1) is a mixture of ethanolamides of coconut acid (q.v.) that conforms generally to the structure shown in Figure 1, where the radical, RCO-, represents the fatty acids derived from coconut oil (Wenninger and McEwen 1997). According to Nikitakis and McEwen (1990), Cocamide MEA contains 82–88% amide.

Other names for Cocamide MEA include Amides, Coco, *N*-(2-Hydroxyethyl)-; Coco Monoethanolamide; Coconut Fatty Acid Monoethanolamide; Cocoyl Monoethanolamine; Equex AEM; *N*-(2-Hydroxyethyl) Coco Fatty Acid Amide; Monoethanolamine Coconut Acid Amide (Wenninger and McEwen 1997); Coconut Oil, Monoethanolamide; Coconut Oil Fatty Acids, Monoethanolamide; and Coconut Oil Fatty Acid Ethanolamide (Chemline 1995).

Cocamide MEA is a tan, granular solid that is water-soluble. The pH of a 10% aqueous solution of Cocamide MEA is 9.5–10.5. The compound has acid and alkali values of 1 (maximum) and 10–20, respectively. Cocamide MEA melts at 60–64°C (Nikitakis and McEwen 1990).

Chemical and Physical Properties

Cocamide DEA is very stable in neutral, moderately alkaline, or acid systems, but is subject to hydrolysis at high concentrations of mineral acids and alkali (Andersen 1996).

Received 25 February 1999; accepted 12 May 1999.

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International Journal of Toxicology, 18(Suppl. 2):9–16, 1999

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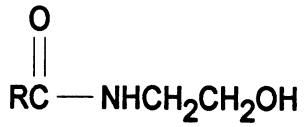

FIGURE 1
Chemical formula for Cocamide MEA, where the radical, RCO-, represents the fatty acids derived from coconut oil (Nikitakis and McEwen 1990; Wenninger and McEwen 1997).

The primary constituents of Coconut Oil are trimyristin, trilaurin, tripalmitin, tristearin, and various other triglycerides. About 90% of the oil is saturated. Coconut Acid is a mixture of fatty acids derived from Coconut Oil by hydrolysis; the fatty acid composition is the same as that for Coconut Oil. Due to the high degree of saturation, Coconut Oil undergoes little change in melting point and consistency following hydrogenation, and is resistant to atmospheric oxidation (Elder 1986a).

MEA is the amino alcohol formed by aminating ethylene oxide with ammonia and replacing one of the ammonia hydrogens with an ethanol group. MEA reacts at room temperature with fatty acids to form ethanolamine soaps, and will react at temperatures between 140 and 160°C with fatty acids to form ethanolamides. The ethanolamines can act as antioxidants in the autoxidation of fats of both animal and vegetable origin. MEA has not, as yet, been found to form a stable nitrosamine; however, MEA can react with an aldehyde to form DEA, which can then be nitrosated to form N-*nitrosodiethanolamine (Elder 1983).*

Method of Manufacture

Cocamide DEA is produced by the condensation of DEA with coconut fatty acids or their esters. It has also been produced by the reaction of refined coconut oil with DEA in the presence of a sodium methoxide catalyst, yielding Cocamide DEA, 10% glycerine, and 5% coconut fatty acid ester amide (Andersen 1996).

Coconut Oil is obtained from copra, where it is present in quantities of 60–70%, and from the kernels of the seeds of Cocos nucifera. The expressed material has a water content of 4–10%. Coconut Acid is derived from Coconut Oil by hydrolysis and isolation of the fatty material, which is then distilled (Elder 1986a).

Impurities

Coconut Oil is usually quite low in color bodies, pigments, phosphatides, gums, and other nonglyceride substances commonly found in much larger quantities in other vegetable oils. It may contain free fatty acids and low concentrations of sterols, tocopherol, and squalene. The presence of approximately 150 ppm lactones (a series of δ-lactones with 6, 8, 10, 12, and 14 carbon atoms) provides the characteristic coconut flavor. Crude samples of Coconut Oil contain traces of polycyclic aromatic hydrocarbons, particularly when the copra is smoke-dried. Aflatoxin (secondary metabolite of the mold Aspergillus flavus*) contamination of raw and dried copra have been reported (Elder 1986a). MEA contains a small amount of DEA (Elder 1983).*

USE

Cosmetic

Cocamide MEA serves as a surfactant—foam booster and aqueous viscosity-increasing agent—in cosmetic formulations (Wenninger and McEwen 1997). Data submitted to the Food and Drug Administration (FDA) in 1996 stated that Cocamide MEA was used in 285 cosmetic product formulations, listed in Table 1 (FDA 1996). The cosmetic industry is no longer required to submit concentration of use data to the FDA (FDA 1992). Data submitted in 1984 stated that 0–0.1% to 10–25% Cocamide MEA was used in cosmetic formulations, with the majority of products containing 1–5% Cocamide MEA (FDA 1984).

TABLE 1
Cosmetic formulation data on Cocamide MEA (FDA 1996)

Product category	Total no. formulations in category	Total no. of formulations containing ingredient
Baby shampoos	23	1
Bath oils, tablets, and salts	147	4
Bubble baths	211	12
Other bath preparations	166	11
Shampoos (noncoloring)	972	131
Tonics, dressings, and other hair grooming aids	604	1
Other hair preparations	395	2
Hair dyes and tints	1612	77
Hair shampoos (coloring)	29	5
Other hair coloring preparations	71	2
Blushers (all types)	277	1
Bath soaps and detergents	372	16
Deodorants (underarm)	303	3
Douches	19	2
Other personal cleanliness products	339	3
Shaving cream	158	5
Shaving soap	3	1
Cleansing	820	14
Body and hand (excluding shaving)	1012	1
Other skin care preparations	810	2
1996 total		**294**

Noncosmetic

Cocamide MEA has been used to separate mammalian sperm acrosomes for use in cattle artificial insemination programs, either by itself (1%), or in a commercially mixed liquid detergent comprised of sodium tetrapropylene benzene sulfonate, sodium lauryl ether sulfate, and Cocamide MEA (4:1:1) (Gombe, Norman, and Mbogo 1975).

International

Cocamide MEA is listed in the *Comprehensive Licensing Standards of Cosmetics by Category (CLS)* and must conform to the standards of the *Japanese Cosmetic Ingredient Codex (JCIC)*. It can be used without restriction in all CLS categories except eyeliners, lipsticks and lip creams, and dentifrices (Yakuji Nippo, Ltd. 1994).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Intubation studies using rats demonstrated that 60% of a 6 g/kg Coconut Oil dose was absorbed within 6 hours. In clinical studies in which subjects received 50–140 g Coconut Oil over 3 days, digestibility was 98% (Elder 1986a).

MEA is the only naturally occurring ethanolamine in mammals and 11% is excreted in the urine (half-life = 19 days). It is converted to phosphatidylethanolamine in all tissues and is methylated to phosphatidylcholine, even in human arteries. In radioactive studies, it was observed that a coenzyme B_{12}–dependent ethnaolamine deaminase–mediated conversion of MEA to acetaldehyde and ammonia can also occur. Feed studies have demonstrated that ATP can phosphorylate MEA, and researchers have hypothesized that the removal of phosphorylated MEA by its conversion to acetate from acetaldehyde may exert a regulatory effect on phosphatidylethanolamine biosynthesis (Elder 1983).

Antimicrobial Effects

MEA inhibits the growth of a wide variety of microorganisms. The concentration required to inhibit growth varies with genus and species. MEA also has some antimycotic activity when applied to the skin of guinea pigs (Elder 1983).

Pharmacodynamic Effects

Administration of 60 mg/kg/day MEA to albino rats with experimentally induced coarction of the aorta for 30 days resulted in elevated levels of phosphatidylethanolamine, phosphatidylcholine (lecithin), and phosphatidylserine in the myocardium. These results may have been produced by inhibition of the development of cardiac insufficiency due to MEA-induced metabolic changes. MEA inhibited the action of purified acetylcholinesterase obtained from bovine erythrocytes. MEA stimulated the activity of purified aspartate transaminase from porcine heart and decreased the enzyme's action in rabbit kidney and heart following oral or intravenous administration. Additionally, intravenous administration of MEA increased the levels of aspartate and glutamate in the kidneys and decreased the levels in the brain of rabbits. Alanine transaminase activity in the kidneys and heart of rabbits was inhibited by MEA. Oral administration of MEA to rats inhibited the activity of alcohol dehydrogenase. MEA can also inactivate and partially dissociate β-galactosidase from Escherichia coli. *MEA can affect the metabolism of catecholamines by increasing norepinephrine and decreasing epinephrine concentrations in the hearts of rats after intraperitoneal injection of 10 mg/kg. An injection of 25 mg/kg had the opposite effect. Also, MEA strongly inhibited the in vitro conversion of proparathyroid hormone to parathyroid hormone. Other effects of MEA administration include the increase of serum albumin and total protein concentrations when given to castrated rams in subchronic oral studies; the increase of RNA in the kidneys, heart, and brain of rabbits; the decrease of DNA in the heart and brain of rabbits; increased myocardial contractility in rats; increased atrial rats and force of contraction in rabbit atria; and increased glycogen, ATP, and ascorbic acid concentrations in the liver, kidneys, brain, and heart of rats (Elder 1983).*

ANIMAL TOXICOLOGY

Acute Toxicity

Undiluted Coconut Oil was judged nontoxic by ingestion when 10 rats were administered 5 g/kg by gavage. No deaths occurred during the 7-day observation period as a result of treatment (Elder 1986a).

The acute oral LD_{50} of undiluted Cocamide DEA in male and female Sprague-Dawley rats was 12.2 g/kg (12.4 ml/kg). The 95% confidence limit was 10.7–14.4 ml/kg. Tests on formulations containing 10% Cocamide DEA and 12% Cocamide DEA had LD_{50}s of >5 g/kg and >5 ml/kg, respectively (Elder 1986b).

MEA has an acute oral LD_{50} in rats of 1.72–2.74 g/kg and was deemed slightly toxic. In an oral corrosivity study using four rabbits, 0.229 g/kg (0.210 ml) of a hair preparation containing 1.6% DEA, 5.9% MEA, and 3.2% sodium borate was placed, undiluted, on the posterior tongue surface. The rabbits were then allowed to swallow. Two each were killed at 24 and 96 hours. No observable abnormalities were observed at gross and microscopic examination, and the preparations were found to be neither irritating nor corrosive under the conditions of this test (Elder 1983). The mouse acute intraperitoneal LD_{50} of MEA was 1.05 g/kg (Elder 1983).

Short-Term Dermal Toxicity

In a 4-week dermal toxicity study, five products, including a shaving cream containing 1.92% Cocamide DEA, were evaluated. Forty-eight New Zealand White rabbits were allotted into six groups of eight animals (four male and four female).

Each rabbit received daily applications (500 mg/kg) of the test material 5 days/week to a shaved area of the back. The site was abraded in four rabbits and intact in the remaining four. Four rabbits per sex served as controls. Moderate erythema, wrinkling, cracking, and dry skin were noted during the first week and continued throughout the study. Skin irritation was observed at both intact and abraded sites. Blood glucose concentrations and serum alkaline phosphatase activities were significantly greater and blood urea nitrogen values were significantly smaller than control values. All other observed parameters were comparable to controls and no systemic effects were attributed to treatment with the shaving cream (Elder 1986b).

Subchronic Toxicity

The subchronic dermal toxicity of Cocamide DEA was evaluated using male and female Fischer 344 rats and B6C3F1 mice. Cocamide DEA was applied to the skin for up to 13 consecutive weeks at doses of 25–400 mg/kg/day (rat) and 50–800 mg/kg/day (mice). Test concentrations were 30–485 mg/ml (rat) and 20–320 mg/ml (mice) in 95% ethanol. Dermal application of Cocamide DEA was associated with microscopic lesions in the skin of male and female F344 rats and in the kidneys of female rats. Treatment-related microscopic lesions were observed in the skin of B6C3F1 mice. In both species, the skin lesions tended to have a dose response with regard to the incidence and severity of the changes present. Renal tubule regeneration was increased in female rats given 200–400 mg/kg/day of Cocamide DEA (Andersen 1996).

A diet containing 25% Coconut Oil was fed to 12 male and 13 female Wistar rats. Eight rats were fed stock feed and served as controls. Three rats of each sex were killed at 15, 30, 60, and 90 days; tissues were microscopically examined and the hepatic lipid content was determined. The treatment group had a progressive increase in fat content of the liver, 20–30% higher than controls by the end of the study. Fatty change of the liver was slight and no other pathological changes were observed (Elder 1986a).

A subchronic percutaneous application study using rats resulted in nonspecific microscopic changes in the heart and lung after administration of 4 mg/kg/day MEA. Effects noted were fatty degeneration of the liver and focal necrosis (Elder 1983).

Inhalation studies (90 days) in which dogs and rodents were exposed to 12–26 ppm MEA did not result in any deaths. Skin irritation and lethargy were seen in dogs, guinea pigs, and rats continuously exposed to 5–6 ppm MEA. Some deaths occurred as a result of the inhalation of 102 ppm MEA vapor in dogs at 25 days and rodents exposed to 66–75 ppm after 24–28 days. Exposure to 66–102 ppm MEA caused behavioral changes, pulmonary and hepatic inflammation, hepatic and renal lesions, and hematologic changes in dogs and rodents (Elder 1983).

Dermal Irritation

Kastner (1977) compared the topical irritancy potential of fatty or fat-derived cosmetic ingredients, including 50% Cocamide MEA in vaseline on skin of various animals (four animals per species) in 24-hour skin patch tests. Patches were applied to the shaven backs of adult male New Zealand White rabbits, male Pirbright white guinea pigs (average weight 300 g), and male and female adult mutant hairless mice. Porous leucoplastic fixed the patches to the guinea pigs and hairless mice. All testing sites were observed at 24 hours (when the patches were removed) and 48 hours. Any reactions were then scored and placed into reaction classes 1–5, with 5 indicating the highest skin irritation potential. Rabbits had the greatest sensitivity to Cocamide MEA, with a class 3 reaction (slight, with the resulting rash fading). Guinea pigs and hairless mice failed to react to Cocamide MEA, and were classified in the lowest reaction group.

The dorsal area of each of six rabbits was shaved and 0.3 ml 30% Cocamide DEA in propylene glycol was applied via a patch to either an intact or abraded site. The entire trunk of each animal was wrapped in cellophane, and patches remained in place for 23 hours. Test sites were scored for irritation 1 and 49 hours after patch removal. 30% Cocamide DEA was a moderate skin irritant; the primary irritation index (PII) was 3.1 (maximum 8). No control data were available (Elder 1986b).

No skin irritation was observed when undiluted Coconut Oil was applied to the skin of nine rabbits in a 24-hour single-insult occlusive patch test. In a second study using either undiluted or 10% (in corn oil) Coconut Acid, PII scores were 0.13/4.0 and 0.12/4.0, respectively, indicating minimal irritation (Elder 1986a).

Bar soaps containing 13% Coconut Oil were evaluated for skin irritation in 14 separate primary irritation studies. Two sites on New Zealand White rabbits of both sexes were clipped of hair and abraded by four perpendicular epidermal abrasions. A 0.5-M dose of a 5% aqueous solution of the soap was applied under occlusive gauze to the abraded sites for 24 hours. The application sites were scored at 24 and 72 hours. PII scores ranged from 1.6 to 4.0 out of 8.0 (Elder 1986a).

Primary skin irritation tests have suggested that MEA is irritating to rabbit skin. 85 and 100% MEA administered by semiocclusive patch applications to intact and abraded shaved skin (evaluated at 4 hours) resulted in visible destructive alteration of the tissue at the test site (corrosive). 30% MEA applied in the same manner and evaluated at 4 and 24 hours had the same result, as well as necrosis at 24 hours (corrosive). When 10 0.1-ml open applications of 1–100% MEA to the ear over 14 days and 10 24-hour semioccluded patch applications were made to the shaved abdomen, it was observed that 10% or higher was corrosive to the skin, >1% was extremely irritating, and 1% was irritating. MEA was thereby classified as "extremely corrosive to the skin" (Elder 1983).

Ocular Irritation

A single 0.1-ml aliquot of 30% Cocamide DEA in propylene glycol was instilled into the conjunctival sac of one eye of each of three female rabbits. The eyes were examined 1 hour after instillation and daily for 7 days thereafter and were scored by

the Draize scoring system. Maximum scores for the 1-hour and day-3 readings were the only ones reported. Irritation scores for the iris and cornea were 0, and the maximum conjunctival score was 6 at 1 hour and 4 at day 3. All effects subsided by day 4. The cumulative ocular irritation rating was not reported, but 30% Cocamide DEA was at least a mild ocular irritant (Elder 1986b).

A modified Draize test was used to test a mixture of Cocamide DEA and DEA at effective concentrations of >0.6% and >0.3%, respectively. The highest mean score was reported on day 3 (57.67). On day 7, a mean score of 37 was reported. The test material was deemed a severe ocular irritant due to continued corneal damage in all three New Zealand white rabbits treated (Andersen 1996).

Undiluted Coconut Oil instilled into the conjunctival sac of each of 12 rabbits (6 per group). Without subsequent rinsing of the eyes, maximum irritation scores of 2 and 1 were reported for the two groups (maximum 110). Coconut was considered a minimal eye irritant (Elder 1986a).

Undiluted Coconut Acid caused mild irritation (8/100 and 9/110) in two tests using three groups of six rabbits each. The eyes were considered normal by the 4th day. In one test, minimal irritation was observed (1/110), and the eyes returned to normal by the 3rd day (Elder 1986a).

A 0.2-ml dose of MEA (30% in water) instilled into the conjunctival sac of each of six rabbits (rinsed after 15 seconds) caused slight discomfort, slight conjunctival irritation, and slight corneal clouding (healed by 48 hours). 1, 5, and 100% MEA applied to the corneal center of rabbits (0.005 ml while lids retracted; lids released after 1 minute) produced scores of ≤5.0, >5, and >5, respectively, out of 20 points, when scored at 18 and 24 hours. 5.0 is the score representative of severe injury; necrosis was visible after staining and covered ~75% of the corneal surface. In a third test, a hair preparation containing 1.6% DEA, 5.9% MEA, and 3.2% sodium borate was instilled (0.1 ml) into the conjunctival sac of each of nine rabbits. Three eyes were rinsed after 30 seconds, and all eyes were examined at 24, 48, and 72 hours, and 4 and 7 days. The maximum average irritation score for both rinsed and unrinsed eyes was 0.7 on the Draize scale (Elder 1983).

Skin Sensitization

A Magnusson-Kligman Maximization test using 10 female Dunkin Hartley DLA guinea pigs was used to determine the skin sensitization potential of 5% Coconut Oil. Two injections each of 50% aqueous Freund's complete adjuvant, 5% Coconut Oil in propylene glycol, and 5% Coconut Oil in 50% Freund's adjuvant were made to separate sites on the back in the induction phase. Control animals received injections of the vehicles only. One week after induction, 5% sodium lauryl sulfate in petrolatum was applied to each induction site. A booster of 100% Coconut Oil was applied to the same sites 24 hours later. Control animals received 5% sodium lauryl sulfate in petrolatum and, as the booster, full strength petrolatum. All guinea pigs were wrapped occlusively for 48 hours. Two weeks after the topical booster, the guinea pigs were challenged with topical applications of 50% and 100% Coconut Oil and wrapped with an occlusive patch, which was removed after 24 hours. Challenge sites were evaluated 48 and 72 hours after the beginning of the challenge. Coconut Oil was nonirritating and failed to produce an allergic response (Elder 1986a).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

A composite hair dye and base containing 22% MEA was given to 60 female rats at concentrations between 0–7800 ppm in the diet from days 6–15 of gestation. The rats were killed on day 19. No evidence of adverse effects were observed in the rats or their pups. No differences were noted in the average number of implantation sites, live pups, early or late resorptions per litter, or females with one or more resorption sites. Thirty male rats were fed the same amounts of MEA for 8 weeks prior to mating and during mating to 60 female rats fed a basal diet. Sixty female rats were fed the treated diet 8 weeks prior to mating (to 30 males fed basal diet) through day 21 of lactation. No treatment-related differences in male and female fertility were detected compared to controls (Elder 1983).

No evidence of teratologic effects were observed in the fetuses of artificially inseminated rabbits that were exposed by gavage to 0–19.5 mg/kg/day MEA in a hair base and dye. Fetal survival was not adversely affected and no gross abnormalities were seen in the fetuses after the does were killed on day 30 of gestation (Elder 1983). The incubation of chicken eggs with 0.03% MEA increased the number of eggs with visible blastodisks, the synthesis of proteins, fats, and carbohydrates, and the number of hatching chicks. Peroxidase activity and the number of organic peroxide molecules in the blood, liver, and homogenates of chick embryos were decreased (Elder 1983).

MUTAGENICITY

Blevins and Taylor (1982) screened 25 cosmetic ingredients, including Cocamide MEA (50 mg/ml diluted to the test concentration) in distilled water, with the *Salmonella typhimurium*/microsome test using *S. typhimurium* strains TA93, TA100, TA1535, TA1537, and TA1538. Negative controls were water, ethanol, dimethyl sulfoxide (DMSO), and no treatment. Positive controls were 2-aminoanthracene, 4-nitro-*o*-phenylene diamine in DMSO, sodium azide in water, and 9-aminoacridine in ethanol. In a screening spot test, Cocamide MEA (50 μg/plate) was mutagenic only in strain TA100 with Aroclor 1254-induced S9 liver homogenates from male Sprague-Dawley rats. In the other strains, and without S9 activation (including TA100), Cocamide MEA was not mutagenic.

In a plate incorporation assay within the same study, Cocamide MEA was tested at 5, 0.5, 0.05, and 0.005 mg/plate with and without metabolic activation. Cocamide MEA gave approximately a twofold increase in the number of revertants over the ethanol counts in TA1535; however, a dose-related increase was

not demonstrated. Cocamide MEA falsely appeared to be mutagenic at the high dose concentrations (0.5 and 0.05 mg/plate). Plate counts were several-fold greater than those of the solvent controls, but there was no background lawn of unreverted bacteria. When several of the "revertant" colonies were transferred to minimal glucose agar, they failed to grow, demonstrating that they were not revertants. The investigators attributed this to the toxicity of the dose concentrations used: most of the bacteria were killed, and as a result, more histidine was available for utilization by the surviving unreverted mutants. Also, at 5 mg/plate Cocamide MEA, a precipitate formed in all plates tested, such that they could not be counted (Blevins and Taylor 1982).

Cocamide DEA was not mutagenic in the Ames Test, with or without metabolic activation. Cocamide DEA induced sister chromatid exchanges in Chinese hamster ovary cells with metabolic activation, but did not induce chromosomal aberrations with or without metabolic activation. In a more recent study, Cocamide DEA did not induce either sister chromatid exchanges or chromosomal aberrations, with or without activation. When tested in L5178Y mouse lyphoma forward mutation assays, both negative and inconclusive results were noted (Andersen 1996).

MEA was not mutagenic in the Ames test using S. typhimurium *strains TA100 and TA1535, with or without metabolic activation (Elder 1983).*

CARCINOGENICITY

High concentrations of dietary fat promoted the development of mammary tumors induced in rats by 7,12-dimethylbenz(a)-anthracene. Coconut Oil, a saturated fat, was less effective than polyunsaturated fats (Elder 1986a).

CLINICAL ASSESSMENT OF SAFETY

MEA inhalation by humans has been reported to cause immediate allergic responses of dypsnea and asthma, as well as clinical signs of acute liver damage and chronic hepatitis (Elder 1983).

Skin Irritation

Kastner (1977) evaluated the topical irritancy of 50% Cocamide MEA (in vaseline) for human skin. Four volunteers each received a patch containing the test substance to the upper arm. All sites were observed at 24 hours, when the patches were removed, and at 48 hours. Reactions were rated between classes 1–5, with class 5 having the greatest irritation. No positive responses were observed.

One hundred and four women participated in an in-use study to determine the safety and efficacy of a shampoo containing 2% Cocamide DEA. Each subject was patch tested on the upper arm with the aqueous shampoo, 15 ppm (in water) of the shampoo's preservative system, and 5% shampoo fragrance in mineral oil. Irritation was scored 48 hours after application, when the patches were removed. The subjects then used the shampoo daily for 87 days. Ten days after the final use, challenge patches were applied using the same procedure as the initial patches, except the preservative concentration was increased to 50 ppm and an additional scoring for reactions was made 24 hours after patch removal. No reactions were observed to the preservative or fragrance patches. Eleven subjects reacted to the 2% shampoo initial patch; eight had mild erythema (1+ scores on a 0–4 scale), one had intense erythema (2+), and two subjects had erythema and edema (3+). 24 panelists had irritation scores of 1+ (18/24), 2+ (3/24), and 3+ (3/24) 48 hours after challenge patch application of the shampoo. Thirty subjects had 1+ (25/30) or 2+ (5/30) irritation scores at the second challenge reading. The shampoo was considered an irritant but not a sensitizer (Elder 1986b).

A bar soap containing 13% Coconut Oil was evaluated for skin irritation using standard Draize procedures. A 1% aqueous solution of the soap was applied using occlusive patches to the forearms of 106 subjects over a 3-week period. Very minimal skin reactions were recorded and the researchers concluded that the soap was not hazardous under conditions of normal use. In a similar test (bar soap with 13% Coconut Oil) using 72 panelists over 2 weeks, investigators reported no unusual irritation responses under normal conditions of use. Soap chamber tests employing Duhring chambers applied to the forearm were conducted using 8% aqueous suspensions of bar soaps containing 13% Coconut Oil. One 24-hour patch and four 6-hour patches were applied over 5 days. In one test using 10 panelists, the soap was moderately irritating, and researchers concluded that the soap was not hazardous under normal use conditions. In a second soap chamber test, minimal irritation was noted among members of the 10-subject panel (Elder 1986a).

Skin Sensitization

Cocamide DEA has been classified as a definite occupational allergen in the hairdressing, medical, fitter, food handling, printing, and cleaning groups. Cocamide DEA exposure produced allergic contact dermatitis in a number of occupational studies. Various concentrations of Cocamide DEA were tested in predictive patch tests; concentrations up to 10% did not produce adverse effects (Andersen 1996).

No erythematous reactions were observed in 103 panelists during a repeat-insult predictive patch test in which a tanning butter containing 2.5% Coconut Oil was applied (Elder 1986a).

A repeated-insult patch test was performed using 0.3 ml of a hair preparation (1.6% DEA, 5.9% MEA, and 3.2% sodium borate) in which an occlusive patch was placed on the forearm for 48 hours during a pretest. In the induction phase of the test, five 48-hour occlusive patches were used. After a 10-day non-treatment period, then a 48-hour challenge patch was applied. Reactions were scored on a scale from 0–3 at patch removal and after 24 hours. The test material was irritating during the pretest. No reactions were observed during the induction and challenge phases; no evidence of contact sensitization was observed in any

a plate incorporation assay, Cocamide MEA at 0.005–5 mg/plate was toxic to the bacterial test strains. In one Chinese hamster ovary cell assay, Cocamide DEA induced sister chromatid exchanges with metabolic activation. In another assay, the results were negative, both with and without activation. In the former set of assays, Cocamide DEA did not induce chromosomal aberrations either with or without metabolic activation. Both negative and inconclusive results were noted for Cocamide DEA in the L5178Y mouse lymphoma forward mutation assay.

In clinical studies, Cocamide MEA at a concentration of 50% was not a human skin irritant in a single-insult patch test. Cocamide DEA at a concentration of 2% in shampoo caused irritation, but was not a sensitizer. No adverse effects were observed during predictive patch tests of a surfactant containing 10% Cocamide DEA. Soap containing 13% Coconut Oil caused minimal irritation when applied to the skin as a 1% aqueous solution. Coconut Oil was not a human skin sensitizer. A cosmetic formulation containing approximately 0.03% MEA was irritating to the skin, but was nonsensitizing, in repeated-insult patch tests. Bar soaps containing 13% Coconut Oil were not phototoxic or photosensitizing.

Cocamide DEA is classified as a known occupational allergen that causes allergic contact dermatitis. However, no adverse effects were reported in patch tests using up to 10% of the test compound. Inhalation of MEA by humans has resulted in dyspnea and asthma, as well as clinical signs of acute liver damage and chronic hepatitis.

DISCUSSION

The CIR Expert Panel has previously evaluated the safety of Cocamide DEA, MEA, and Coconut Oil and its derivatives and concluded that these ingredients are safe for use as cosmetic ingredients. Cocamide DEA was originally reviewed by the CIR Expert Panel in 1986 and was concluded safe up to 50%. The Expert Panel reevaluated the safety of Cocamide DEA in 1994 after occupational studies indicated that the ingredient can have sensitizing potential. Upon review of new sensitization data, the Expert Panel clarified the original conclusion, recognizing that "while occupational exposure to Cocamide DEA can result in sensitization, cosmetic use does not present the same concern." The Panel was concerned about the inhalation toxicity of MEA. The CIR Expert Panel concluded that Cocamide DEA is safe as used in rinse-off products and safe at concentrations up to 10% in leave-on products, but should not be used as an ingredient in formulations in which *N*-nitroso compounds are formed or in products intended to be aerosolized.

Despite the lack of available safety data on Cocamide MEA, the Expert Panel concluded that the data on those ingredients previously reviewed, particularly Cocamide DEA, were adequate to support the safety of Cocamide MEA in cosmetics, with the same concentration limits and the caveat to avoid using Cocamide MEA in formulations intended to be aerosolized or in formulations containing *N*-nitrosating agents.

CONCLUSION

On the basis of the animal and clinical data presented in this report, the CIR Expert Panel concludes that Cocamide MEA is safe as used in rinse-off cosmetic products and safe at concentrations up to 10% in leave-on products. Cocamide MEA should not be used as an ingredient in cosmetic products containing *N*-nitrosating agents, or in product formulations intended to be aerosolized.

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[2]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, N.W., Suite 310, Washington, DC 20036, USA.

of the 25 subjects. The same hair preparation was tested using 0.2 ml of the material applied to patches on the back for 23 hours daily for 21 days. Reactions were scored daily on a scale of 0 to 7. In the panel of 12 females, the subjects had 4, 3, and 225 scores of barely perceptible erythema, definite erythema, and erythema and papules, respectively. The test compound was deemed an experimental cumulative irritant (Elder 1983).

A dyeless noncommercial base formulation (11.47% MEA) was diluted to 25% in alcohol and 0.3 ml was applied to the upper arms of 165 volunteers 3 days/week for three weeks using 24-hour semiocclusive patches. Sites were evaluated 24 and 48 hour after patch removal. Challenge applications were made on the same site and a virgin site after 15–17 days. Scores (out of 5) were made 24 and 72 hours later. There were 19 instances of mild erythema and one each of definite papular response, definite edema, and definite edema and papules, respectively, during induction. No adverse reactions were observed at challenge; the test substance was therefore an irritant, but not a contact sensitizer (Elder 1983).

Phototoxicity

Aqueous solutions (3%) prepared from bar soaps containing 13% Coconut Oil were applied using occlusive patches to the tape-stripped backs of 10 volunteers over a 6-week period. After each application, the treatment sites were exposed to an inspectrolamp for 45 minutes. After UVA exposure, the area was exposed to about two thirds of the Minimal Erythemal Dose from an air-cooled Kromayer lamp. No evidence of phototoxicity was observed (Elder 1986a).

Photosensitization

Bar soaps (13% Coconut Oil) were tested as 3% aqueous solutions in a photosensitization test using 10 panelists. Patches containing 0.2 ml were applied to stripped skin three times per week for 24 hours over a 3-week period. Sites were exposed to a Wood's lamp for 40 minutes and a sun lamp for 15 minutes after each application. Following a 2-week nontreatment period, duplicate challenge patches were applied. No evidence of photosensitization was observed. A similar soap containing 13% Coconut Oil (1% and 5% aqueous solutions) was tested using 52 subjects. Occlusive patches containing 0.4 ml of the test solutions were applied to the arms three times per week for 3 weeks. Sites were exposed to sunlight for 30 minutes 24 hours after application. After a 2-week nontreatment period, duplicate challenge patches were applied. Sun exposures were made 24 hours later. No photosensitization reactions were noted (Elder 1986a).

SUMMARY

Cocamide MEA is a mixture of ethanolamines of fatty acids derived from coconut oil. It functions as a surfactant—foam booster and aqueous viscosity-increasing agent—in cosmetic formulations. In 1996, Cocamide MEA was reported to be used in 285 cosmetic formulations of various product categories.

Data on the chemical and physical properties, method of manufacture, impurities, absorption, distribution, metabolism, and excretion of Cocamide MEA were not available. Data have been included from previous CIR safety assessments on Coconut Oil and its derivatives, MEA, and Cocamide DEA.

MEA is the only naturally occurring ethanolamine in mammals. MEA can be converted to ammonia and acetaldehyde, and can be reacted with an aldehyde to form DEA. DEA is readily nitrosated to form *N*-nitrosodiethanolamine, a carcinogen in laboratory animals. MEA has not yet been found to form a stable nitrosamine.

The acute oral LD_{50}s of Cocamide DEA in rats ranged from >5 g/kg to 12.2 g/kg at concentrations of 10–12% and 100%, respectively. Undiluted Coconut Oil did not cause mortality in acute toxicity studies using rats. The acute oral LD_{50} of MEA was 1.72–2.74 g/kg in rats; MEA was deemed slightly toxic. MEA was noncorrosive in an oral study using rabbits. The acute intraperitoneal LD_{50} of MEA in mice was 1.05 g/kg.

A formulation containing 1.92% Cocamide DEA caused irritation but no systemic effects in a 4-week dermal toxicity study using rabbits. Coconut Oil (25% in feed) administered to rats for up to 90 days produced no signs of toxicity. Subchronic percutaneous application of 4 mg/kg/day MEA to rats caused nonspecific histologic changes of the heart and lung tissue, fatty degeneration and focal necrosis of the liver. MEA vapor was highly toxic when concentrations of 66–102 ppm were continuously inhaled by dogs and rodents during 90-day studies. Signs of toxicity included behavioral changes, pulmonary and hepatic inflammation, renal and hepatic damage, and increased mortality.

Cocamide MEA at a concentration of 50% was nonirritating to the skin of guinea pigs and mice and was slightly irritating in rabbits during a single-insult patch test. Cocamide DEA at a concentration of 30% was moderately irritating to the skin of rabbits. Undiluted Coconut Oil was a minimal irritant. Soap containing 13% Coconut Oil produced slight irritation. Coconut Oil was nonsensitizing in the Magnusson-Kligman Maximization Test using female guinea pigs. MEA was irritating and corrosive to the skin of rabbits.

Cocamide DEA was at least a mild ocular irritant in rabbits when administered at a concentration of 30%. Undiluted Coconut Oil caused minimal irritation. Undiluted Coconut Acid produced mild ocular irritation. MEA at a concentration of 30% caused slight discomfort, conjunctival irritation, and corneal clouding in rabbits, but these reactions were slight. Severe ocular injury, including necrosis, occurred when 5–100% MEA was applied to the corneal center of rabbits.

Rats given up to 19.5 mg/kg/day by gavage of a hair base and dye containing 22% MEA had no signs of reproductive and developmental toxicity.

Cocamide MEA, Cocamide DEA, and MEA were not mutagenic in the Ames Test, with or without metabolic activation. In

ACETAMIDE MEA	1	03G - Other Eye Makeup Preparations	25
ACETAMIDE MEA	40	05A - Hair Conditioner	121
ACETAMIDE MEA	14	05B - Hair Spray (aerosol fixatives)	23
ACETAMIDE MEA	2	05E - Rinses (non-coloring)	
ACETAMIDE MEA	32	05F - Shampoos (non-coloring)	
ACETAMIDE MEA	21	05G - Tonics, Dressings, and Other Hair Grooming Aids	
ACETAMIDE MEA	2	05H - Wave Sets	
ACETAMIDE MEA	10	05I - Other Hair Preparations	
ACETAMIDE MEA	1	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	
ACETAMIDE MEA	1	08F - Nail Polish and Enamel Removers	
ACETAMIDE MEA	3	10A - Bath Soaps and Detergents	
ACETAMIDE MEA	9	10B - Deodorants (underarm)	
ACETAMIDE MEA	4	12A - Cleansing	
ACETAMIDE MEA	4	12D - Body and Hand (exc shave)	
ACETAMIDE MEA	2	12F - Moisturizing	64
ACETAMIDE MEA	1	12G - Night	84
ACETAMIDE MEA	1	12J - Other Skin Care Preps	148
COCAMIDE MEA	2	01A - Baby Shampoos	
COCAMIDE MEA	2	01C - Other Baby Products	579
COCAMIDE MEA	6	02A - Bath Oils, Tablets, and Salts	521
COCAMIDE MEA	59	02B - Bubble Baths	
COCAMIDE MEA	16	02D - Other Bath Preparations	
COCAMIDE MEA	2	04E - Other Fragrance Preparation	
COCAMIDE MEA	7	05A - Hair Conditioner	367
COCAMIDE MEA	1	05E - Rinses (non-coloring)	
COCAMIDE MEA	346	05F - Shampoos (non-coloring)	
COCAMIDE MEA	4	05G - Tonics, Dressings, and Other Hair Grooming Aids	
COCAMIDE MEA	7	05I - Other Hair Preparations	
COCAMIDE MEA	167	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	
COCAMIDE MEA	3	06D - Hair Shampoos (coloring)	173
COCAMIDE MEA	2	06F - Hair Lighteners with Color	
COCAMIDE MEA	1	06G - Hair Bleaches	
COCAMIDE MEA	2	08G - Other Manicuring Preparations	
COCAMIDE MEA	223	10A - Bath Soaps and Detergents	
COCAMIDE MEA	1	10C - Douches	
COCAMIDE MEA	216	10E - Other Personal Cleanliness Products	
COCAMIDE MEA	2	11E - Shaving Cream	
COCAMIDE MEA	37	12A - Cleansing	
COCAMIDE MEA	6	12D - Body and Hand (exc shave)	33
COCAMIDE MEA	3	12F - Moisturizing	1,008
COCAMIDE MEA	6	12J - Other Skin Care Preps	81
COCAMIDE MEA	1	13C - Other Suntan Preparations	1,122
COCAMIDOPROPYL BE	14	10A - Bath Soaps and Detergents	
COCAMIDOPROPYL BE	4	10E - Other Personal Cleanliness Products	
COCAMIDOPROPYL BE	3	12A - Cleansing	21
LACTAMIDE MEA	1	03G - Other Eye Makeup Preparations	
LACTAMIDE MEA	2	05A - Hair Conditioner	17
LACTAMIDE MEA	4	05B - Hair Spray (aerosol fixatives)	
LACTAMIDE MEA	1	05F - Shampoos (non-coloring)	
LACTAMIDE MEA	10	05G - Tonics, Dressings, and Other Hair Grooming Aids	
LACTAMIDE MEA	1	08F - Nail Polish and Enamel Removers	
LACTAMIDE MEA	1	10E - Other Personal Cleanliness Product	9
LACTAMIDE MEA	2	12D - Body and Hand (exc shave)	21
LACTAMIDE MEA	4	12F - Moisturizing	6
LACTAMIDE MEA	1	12H - Paste Masks (mud packs)	27
LAURAMIDE MEA	2	02B - Bubble Baths	28
LAURAMIDE MEA	2	02D - Other Bath Preparations	

LAURAMIDE MEA	1	04E - Other Fragrance Preparation	35
LAURAMIDE MEA	1	05E - Rinses (non-coloring)	
LAURAMIDE MEA	8	05F - Shampoos (non-coloring)	
LAURAMIDE MEA	41	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	
LAURAMIDE MEA	2	06D - Hair Shampoos (coloring)	
LAURAMIDE MEA	14	10A - Bath Soaps and Detergents	
LAURAMIDE MEA	10	10E - Other Personal Cleanliness Products	
LAURAMIDE MEA	4	12A - Cleansing	
LAURAMIDE MEA	2	12J - Other Skin Care Preps	87
MYRISTOYL/PALMITOY	1	12A - Cleansing	
MYRISTOYL/PALMITOY	3	12F - Moisturizing	
PEG-9 COCAMIDE MEA	1	05A - Hair Conditioner	
STEARAMIDE MEA	5	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	
STEARAMIDE MEA	2	06F - Hair Lighteners with Color	
STEARAMIDE MEA	2	10B - Deodorants (underarm)	
STEARAMIDE MEA	1	12A - Cleansing	10
STEARAMIDE MEA-STE	2	03F - Mascara	
STEARAMIDE MEA-STE	1	05A - Hair Conditioner	
STEARAMIDE MEA-STE	1	12A - Cleansing	
STEARAMIDE MEA-STE	4	12F - Moisturizing	8
TRIDECETH-2 CARBOX.	5	05I - Other Hair Preparations	
TRIDECETH-2 CARBOX.	130	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	
TRIDECETH-2 CARBOX.	53	06H - Other Hair Coloring Preparation	183
TRIDECETH-2 CARBOX.	1	10E - Other Personal Cleanliness Product	189
UNDECYLENEAMIDE M	1	06H - Other Hair Coloring Preparation	
UNDECYLENEAMIDE M	1	10B - Deodorants (underarm)	
UNDECYLENEAMIDE M	1	12E - Foot Powders and Sprays	
PEG-5 COCAMIDE	15	05F - Shampoos (non-coloring)	
PEG-5 COCAMIDE	2	10A - Bath Soaps and Detergents	
PEG-5 COCAMIDE	19	10E - Other Personal Cleanliness Products	
PEG-5 COCAMIDE	3	12A - Cleansing	
PEG-5 COCAMINE	1	06B - Hair Tints	
PEG-6 COCAMIDE	1	02B - Bubble Baths	
PEG-6 COCAMIDE	6	05F - Shampoos (non-coloring)	
PEG-6 COCAMIDE	2	05I - Other Hair Preparations	
PEG-6 COCAMIDE	1	06D - Hair Shampoos (coloring)	
PEG-6 COCAMIDE	11	10A - Bath Soaps and Detergents	
PEG-6 COCAMIDE	1	12A - Cleansing	
PEG-6 COCAMIDE	1	12D - Body and Hand (exc shave)	

Personal Care Products Council
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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: December 8, 2011

SUBJECT: Comments on the Draft Report on the Ethanolamide Ingredients Prepared for the December 12-13, 2011 CIR Expert Panel Meeting

Key Issue

It is not clear that all of the ingredients proposed for this report are appropriate. The Chemistry section (p.2) states: "The ethanolamides consist of covalent, secondary amides, whereby one of the nitrogen substituents is ethanol (or at least an ethanol residue) and the second is a carbonyl attached substituent." Based on the structures provided in Table 1, the following ingredients do not have an ethanol substituent and should not be included in this re-review: Hydroxyethyl Pantothenamide MEA, Stearamide MEA-Stearate, PEG-2 Cocamide, PEG-3 Cocamide, PEG-4 Cocamide, PEG-5 Cocamide, PEG-6 Cocamide, PEG-7 Cocamide, PEG-9 Cocamide MEA, PEG-11 Cocamide, PEG-20 Cocamide, PEG-20 Cocamide MEA and Sodium/MEA-PEG-3 Cocamide Sulfate.

p.1 - In the Introduction, please delete "that was proven safe", as it is not possible to prove that something is safe.

Additional Comments

p.3 - In describing the concentration of use information, please do not use "anti-perspirants". The FDA cosmetic product category is "deodorants (underarm)". In the United States, antiperspirants are considered drugs and are probably not reported to the either the VCRP or Council concentrations of use surveys. Throughout the Cosmetic Use section, please provide the specific FDA product categories associated with the use concentrations from the Council survey.

p.4 - Under the Oral Acetamde MEA summary, if kg represents body weight, >16.9 g/kg and >25 ml/kg are doses not concentrations.

p.10-14, Table 1 - As this is a review of cosmetic ingredients, please include the definitions from the Cosmetic Ingredient Dictionary and Handbook. One footnote could be used for all ingredients that the Dictionary defines by structure.

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p.14, Table 1 - The last ingredient should be "PEG-3" rather than "PPG-3"

p.18-20, Tables 4a and 4b - There are 17 ingredients in Table 4a and 31 ingredients in Table 4b for a total of 48 ingredients. The Introduction of the report indicates that there are total of 50 ingredients in the report. Sodium/MEA-PEG-3 Cocamide Sulfate appears to be one of the ingredients missing from Table 4b. Please identify the other missing ingredient and add it to the appropriate table.

Personal Care Products Council
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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 11, 2012

SUBJECT: Comments on the Tentative Report on Ethanolamides as Used in Cosmetics

p.1, Abstract - "that" needs to be added to the following: "...included 25 additional ethanolamides [that] are secondary carboxamides...]

p.2, 9 - As all of the ingredients currently appear to have an ethanol substituent, is "(or at least an ethanol residue)" still necessary (found in the Chemistry section and the Discussion)?

p.3 - As exposure varies by area of application, rather than using the general terms in the Cosmetic Use section, please use the FDA product categories.

p.3, 10 - To add perspective to the potential inhalation exposure, please include the maximum reported concentration in the product that might be a spray product in both the Cosmetic Use section and the Discussion.

p.5 - The word "gavage" is not a verb ("gavaged" is included in the MEA paragraph under Reproductive and Developmental Toxicity).

p.5 - In the reproductive study of palm oil, what was measured to assess endocrine function? Does this include an assessment of thyroid function?

p.7 - Please include a reference for the Cocamide MEA guinea pig sensitization study.

p.10 - In the first complete paragraph, please correct "hepatogenicity" to "hepatocarcinogenicity"

p.11-13, Table 1 - All of the definitions as given in the *International Cosmetic Ingredient Dictionary and Handbook* should be given in Table 1. Ingredients defined by their structure could identified with a footnote that states that the *Dictionary* defines these ingredients by their structure.

p.14, Table 2 - The publication date for the Ricinoleic Acid report (reference 29) should be 2007 not 2011.

p.15, Table 3 - What type of partition coefficient, e.g., octanol/water, is presented for Cocamide MEA? Is this really the partition coefficient or log P (which is presented for all of the other ingredients)?

p.18, Table 4a - NS under Table 4a can be deleted as all of the ingredients have now been included in a Council concentration of use survey, or removed from the report.

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