Safety Assessment of Fatty Acid Amidopropyl Dimethylamines as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	February 21, 2014
Panel Meeting Date:	March 17-18, 2014

The 2014 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 Lillian J. Gill, DPA. This safety assessment was prepared by Christina Burnett, Scientific Analyst/Writer, and Bart Heldreth, Ph.D., Chemist CIR.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett
Scientific Writer/Analyst
Date: February 21, 2014
Subject: Draft Tentative Report on Fatty Acid Amidopropyl Dimethylamines

In September 2012, the Panel tabled the safety assessment on fatty acid amidopropyl dimethylamines while a dossier including data from additional studies on stearamidopropyl dimethylamine was being prepared under the auspices of the REACH program in Europe. The Panel was informed that the data would be received mid-2013. CIR was not informed by Industry when the data were available, but instead discovered the data through a search of the European Chemical Agency's (ECHA) database. These data have been incorporated into the report and highlighted.

While awaiting these data, the Panel alerted the public that the data in the current safety assessment were insufficient to support the safety of the fatty acid amidopropyl dimethylamine ingredients. The additional data needed included: (1) percutaneous absorption data on cocamidopropyl dimethylamine, and if it is absorbed; (2) reproduction and developmental toxicity data; and (3) sensitization and irritation data on oleamidopropyl dimethylamine at use concentration.

Since September 2012, an irritation study of 1% oleamidopropyl dimethylamine oil has been received and incorporated into the report. No other data have been received. Comments received prior to the September 2012 Panel meeting on the draft tentative safety assessment have been considered. Both the data and the comments are available for your review in this report's package.

If the information now available is sufficient for these ingredients, the Panel should issue a Tentative Safety Assessment with an appropriate discussion/conclusion. If the information is still insufficient, then a Tentative Safety Assessment with an insufficient data conclusion should be issued.

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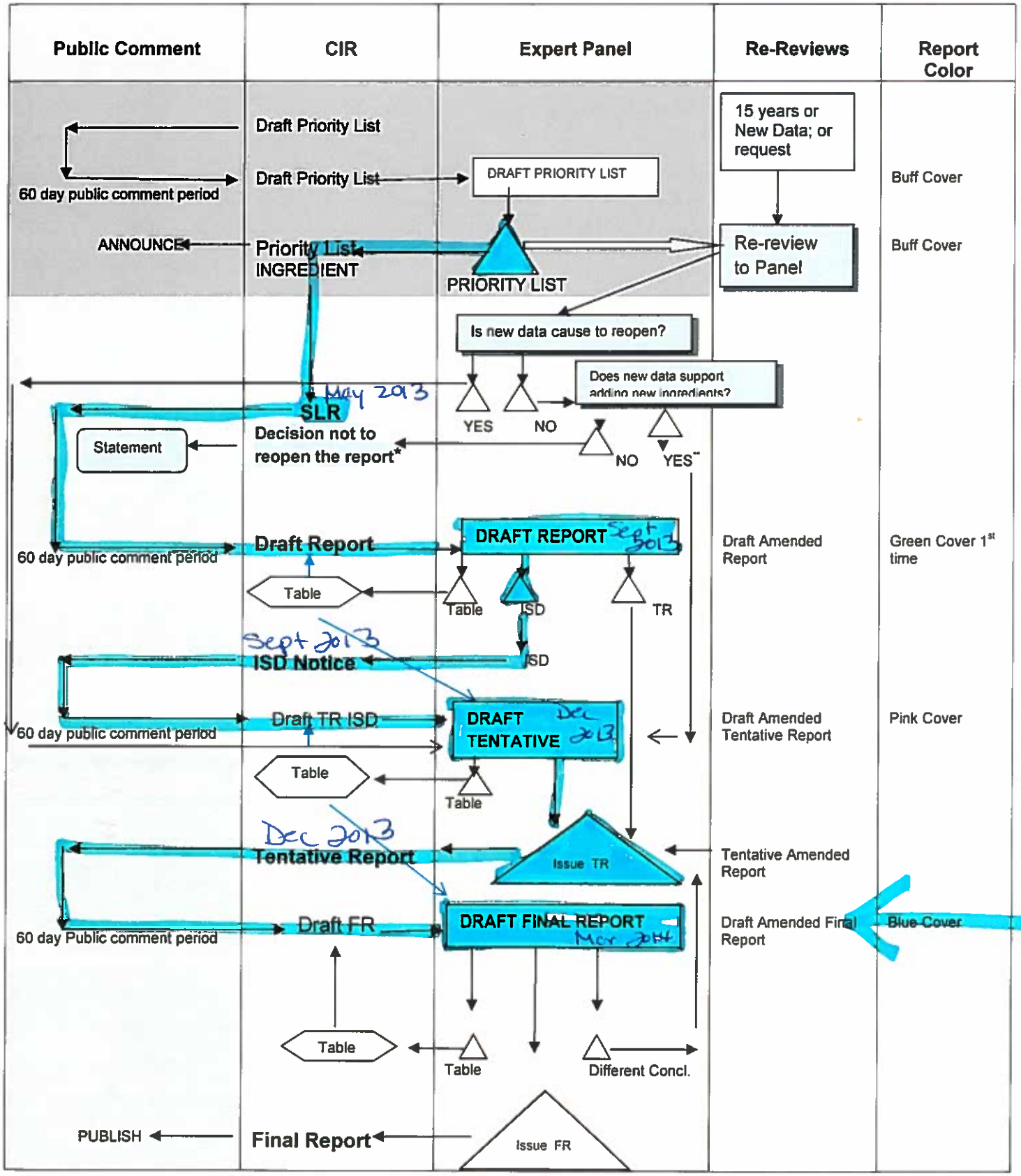
Alkyl Betaines

SAFETY ASSESSMENT FLOW CHART

Mar 2014



Fatty Acid Amidopropyl Dimethylamines History

February 2012 – Scientific Literature Review announced.

June 2012 - The CIR Expert Panel requested additional data to support the safety of fatty acid amidopropyl dimethylamines. The additional data needed are: (1) percutaneous absorption of the ingredient that has the shortest chain fatty acids (e.g., lauramidopropyl dimethylamine), and if it is absorbed; (2) reproduction and developmental toxicity data; and (3) sensitization an irritation data on oleamidopropyl dimethylamine at use concentration.

September 2012 – The Expert Panel tabled the safety assessment on fatty acid amidopropyl dimethylamines while a dossier including data from additional studies on stearamidopropyl dimethylamine was being prepared under the auspices of the REACH program in Europe. The Expert Panel was informed that the data would be received mid-2013. While awaiting these data , the Panel alerted the public that the data in the current safety assessment were insufficient to support the safety of the fatty acid amidopropyl dimethylamine ingredients. The additional data needed included: (1) percutaneous absorption data on cocamidopropyl dimethylamine, and if it is absorbed; (2) reproduction and developmental toxicity data; and (3) sensitization and irritation data on oleamidopropyl dimethylamine at use concentration.

FA Amidopropyl Dimethylamines Data Profile* – March 2014 –
Writer, Christina Burnett

	Reported Use	Chemical Properties	Toxicokinetics	Acute Toxicity	Repeated Dose Toxicity	Reproductive/ Developmental	Genotoxicity	Irritation/ Sensitization – Non-Human	Irritation/ Sensitization - Human	Ocular/ Mucousal
Almondamidopropyl Dimethylamine										
Avocadamidopropyl Dimethylamine										
Babassuamidopropyl Dimethylamine										
Behenamidopropyl Dimethylamine	X	X						X	X	X
Brassicamidopropyl Dimethylamine	X								X	
Cocamidopropyl Dimethylamine	X	X						X	X	
Dilinoleamidopropyl Dimethylamine										X
Isostearamidopropyl Dimethylamine	X									
Lauramidopropyl Dimethylamine	X	X								
Linoleamidopropyl Dimethylamine		X								
Minkamidopropyl Dimethylamine	X									
Myristamidopropyl Dimethylamine		X								
Oatamidopropyl Dimethylamine										
Oleamidopropyl Dimethylamine	X	X						X	X	
Olivamidopropyl Dimethylamine										
Palmitamidopropyl Dimethylamine	X	X								
Ricinoleamidopropyl Dimethylamine		X								
Sesamidopropyl Dimethylamine										
Soyamidopropyl Dimethylamine										
Stearamidopropyl Dimethylamine	X	X	X	X	X	X	X	X	X	X
Sunflowerseedamidopropyl Dimethylamine										
Tallamidopropyl Dimethylamine										
Tallowamidopropyl Dimethylamine										
Wheat Germamidopropyl Dimethylamine										

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

SEARCH STRATEGY FOR FA Amidopropyl Dimethylamines (Performed by Christina Burnett)

January 2012: SCIFINDER search for under the answer set for Fatty Acid APDMA (14 substances):

- Initial search for "adverse effect, including toxicity" yielded 11 references.

Search Terms	TOXLINE (excluding PUBMED, English only)	PUBMED
January 2012		
Amidoamine	5	535
Amidopropyl Dimethylamine	0	1
7651-02-7	1	1
20182-63-2	1	0
60270-33-9	0	0
68140-01-2	2	0
67799-04-5	0	0
3179-80-4	1	0
81613-56-1	1	0
68953-11-7	0	0
45267-19-4	0	0
109-28-4	10	7
39669-97-1	0	0
20457-75-4	0	0
68188-30-7	0	0
68650-79-3	1	0
68425-50-3	0	0

Total references ordered: 17

Search updated July 20, 2012. No new relevant data discovered.

Search updated January 10, 2014. No new relevant data discovered.

September 10-11, 2012 Panel Meeting

Belsito's Team

DR. BELSITO: So, fatty acid amidopropyl dimethylamines.

So, I guess this came in wave two. A supplier indicated additional studies in stearamidopropyl dimethylamine for the REACH dossier would be available by May of 2013.

And also, the consortium that is preparing the dossier for REACH is telling us that the data for stearamidopropyl dimethylamine does not support, in their opinion, a read across approach to other alkyl amidopropyl dimethylamines, particularly to the shorter chain fatty acids, because of the sensitization potential of the shorter chains.

So, the question is, do we table this for the REACH approach? Do we split out a certain group of amidopropyl dimethylamines? And at what chain level do we split them out?

You know that I had previously asked for sensitization data on oleamidopropyl dimethylamine because I see that in my clinic with eyelid dermatitis from shampoos.

I don't even know is oleamidopropyl bigger than stearamidopropyl?

DR. LIEBLER: It's the same length, it's just olea then has a single has one double bond then a chain.

DR. BELSITO: I see.

DR. SNYDER: It's easy when (inaudible) Finish his sentence and you already have the answer.

DR. BELSITO: But, you guys got the same information as I did in wave two, so

DR. SNYDER: Well, I mean, for me the issue was that this report has no absorption, distribution, metabolism, and excretion, or tox studies to support safety. But the CAPB report didn't have absorption, distribution, metabolism, and excretion, but we did have lots of tox data. And so we used the tox data to alleviate the lack of absorption data.

But in this report, we don't have either one. So that group is a little more problematic, I think. Because we don't have any data sets.

DR. BELSITO: So, do I mean, I guess the question is, do we go "insufficient," for all the reasons that we originally were "insufficient?" Do we I mean, one way or the other, I think we have to respond to the consortium that is writing the dossier for REACH on this stearamidopropyl dimethylamine.

And, basically, what they're telling us is that you can't link this, or lump it, with some of the other alkyl amidopropyl dimethylamines that you're going to lump it with.

So, you know, do we split this out as an individual ingredient? Do we say, okay, you know, we're going to take these amidopropyl dimethylamines that are bigger than 10 carbons, and consider them in one group, and smaller I mean, how do we handle this?

Because, quite clearly, we're going to go either "insufficient," or table it, or create two different documents, or we've got to do something with this report.

DR. LIEBLER: So stearamido is okay.

DR. BELSITO: No. I don't think any of them are okay.

DR. SNYDER: No, we don't know.

DR. LIEBLER: Okay. So then we don't

DR. BELSITO: But they're asking us to wait until, essentially, as I read it, to wait until May of 2013, when they complete the REACH safety dossier.

DR. ANDERSEN: For stearamido dimethylamine

DR. BELSITO: Right.

DR. ANDERSEN: which we believe will address some of the data requests.

DR. BELSITO: Right. And then what they're saying: By the way, you can't use our data to support the data of the shorter chains.

DR. LIEBLER: So the lauramido and all the amidopropyl

DR. SNYDER: We're just we would just be prolonging the inevitable. It's going to be "insufficient," even if we go with

DR. BELSITO: Well, we don't know what they

DR. SNYDER: Because, the REACH, if we can't

DR. BELSITO: I mean, the REACH, depending upon the volume of use, I mean, the sales and the tonnage of use in Europe, the REACH dossier can be very, very extensive. I mean, it's not even like us making judgments. It's an official checklist that you actually have to do the studies.

So even if you could predict that this is a, you know, 500 million kilodalton molecule that, you know, wouldn't get through the mucous membrane of a mouse, if it's sold in so much tonnage, you have to have absorption studies.

DR. LIEBLER: So the REACH document is going to be on stearamidopropyl

DR. ANDERSEN: Right the stearamidopropyl. And it will be required to address repro and developmental toxicity.

DR. LIEBLER: Okay, but only on that compound.

DR. BELSITO: Yes.

DR. LIEBLER: It will not address the other two. So, the issue that's going to help with stearamidopropyl, but it won't help with shorter chain length compounds.

DR. BELSITO: Right.

DR. LIEBLER: And that's one of our "insufficients."

DR. ANDERSEN: Right.

DR. LIEBLER: And we asked for the shortest chain length, which is the lauramidopropyl, and so we'll still end up needing that.

DR. SNYDER: We'll still have (inaudible).

DR. ANDERSEN: Well, you're not going to get it, because it is a sensitizer.

DR. LIEBLER: Okay. Then that makes our job easy, doesn't it.

But then cocamidopropyl, I would have concerns about, because that's mostly C12 and C14.

DR. BELSITO: Well, the question, again, that I will pose is, do we take out stearamidopropyl dimethylamine, and make this one document like we used to do back in the old days, one ingredient at a time?

Do we accept what they're saying, that, you know, C16 to shorter chain fatty acids, or potential increases, and split this document at a C level, say, okay, we're going to look at everything bigger than C12, (inaudible), everything smaller than C12 or C14, or you tell me where.

But I think we need to make that kind of decision and say, okay, you know, we'll split it C whatever and, you know, we'll table the C greater than, pending the REACH dossier in May. And for the ones that are smaller than that C, "they're insufficient for all these reasons."

I mean, I'd like to do that, but I don't know what C I should pick.

DR. LIEBLER: Well, picking a number I mean, if we're going stearamidopropyl's 18. So, we could simply say below 18, it's "insufficient." That would be the simplest thing to do.

But then that's going to that will knock out almost all the compounds.

DR. SNYDER: So we wanted it on, we either wanted dermal absorption on the shortest, lauramido, or we wanted sensitization and irritation on olea?

DR. BELSITO: Oleamidopropyl.

DR. SNYDER: So it's kind of between a rock and a hard spot, really.

DR. LIEBLER: Two different issues.

DR. SNYDER: Two different issues, yeah. And lauramidopropyl is a sensitizer right? So

DR. BELSITO: Well, I mean, oleamidopropyl, people get sensitized to, too. I mean, I don't the question is, you know, I'm obviously seeing diseased people. I'm seeing people who come in with eyelid disease. So, you know, while I can tell you that, you know, when I did a study looking at, you know, what were the sensitizes in people who presented with eyelid dermatitis, it's just you know, it's subject to the same criticism that I gave back to Jim Marks. We're talking about, you know, what were the sensitizers in subjects who had cheilitis? You know, they're not the entire population.

So what I can tell you is that oleamidopropyl dimethylamine sensitizes some people. And people who present with only eyelid dermatitis, it's one of the main causes that I've found, along with nail polish.

But what I can't tell you is what percentage of the population is allergic, and at what level do they become allergic. You know, for all I know, these women could have used undiluted shampoo to remove their eye makeup. I mean, God knows how people become sensitized to things.

But, you know, we just need the data. We need and we need some cutoffs here.

DR. SNYDER: Well, I think it would be better since this is where we're at in this stage of the process, wouldn't it be better to go "insufficient" for dermal absorption across the board? First?

DR. BELSITO: Well, for sensitization. I'm more concerned about sensitization.

DR. LIEBLER: Okay, but I mean, as the overall Panel, we expressed concern about absorption and tox.

DR. BELSITO: Yes.

DR. LIEBLER: As well as sensitization.

DR. BELSITO: Right.

DR. LIEBLER: So, the first two bullets in our discussion were "absorption" and "tox."

DR. BELSITO: Yes.

DR. LIEBLER: And we have neither.

DR. BELSITO: Right.

DR. LIEBLER: So we basically need all those things addressed.

DR. BELSITO: Mm hmm.

DR. LIEBLER: So I think we are in an "insufficient" situation with these.

DR. SNYDER: I think so. And I don't think we have any scientific basis to draw a line, to calculate at what length we're going to cut off.

DR. BELSITO: Yes, I guess we need

DR. SNYDER: So we can't even logically, scientifically, whatever reason, come up with a cutoff, to say, well, we'll be okay above this.

DR. BELSITO: Because we don't know how the absorption varies with chain length.

DR. SNYDER: Right.

DR. LIEBLER: Well, I think we can probably expect that the shortest of these ingredients, the C12, will have the greatest absorption.

DR. BELSITO: Right.

DR. LIEBLER: And that it will decrease going up. But I don't know if that tells you where you would drawn the line. We can't make a guess, or play a hunch, as to where to draw the line, without some data.

DR. BELSITO: Well, clearly, when you look at Table 3, and the frequency of use of these compounds, you know it's interesting, because I don't test for stearamidopropyl dimethylamine, and it could be that my oleamidopropyl dimethylamine people were cross reacting. Because it's really stearamidopropyl dimethylamine that's driving the group 472 uses.

DR. SNYDER: Right.

DR. BELSITO: Up to 5 percent. As opposed to oleamidopropyl, which is 12, up to 1 percent.

So, you know, and if you look at everything else I mean, 3, 8, 31, 21, 23, 24

DR. SNYDER: So why

DR. BELSITO: 36, 37 the rest of the group has uses.

DR. SNYDER: Why did we, then, ask for sensitization on olea, when we should have asked for stearamido?

DR. BELSITO: Because of me. (Laughs.) Mea culpa, mea culpa, mea maxima culpa.

DR. SNYDER: So we really would rather have it on stearamido.

DR. BELSITO: Right.

DR. ANDERSEN: And what we're suggesting is that we believe there's going to be a substantive data set addressing all of the endpoints, because of the reach for the stearamido, and that you'd table it until that time.

But we do expect that no one's going to come forward with laurel data. So how you know, I don't know from a process standpoint whether you can announce I mean, it's only pink, right? So whether you announce "insufficient," or

DR. BELSITO: Well, if we go "insufficient" at this point, you know, it could come up for final review in December. And we're not given I mean, industry is telling us the dossier is out in May.

So I would say, in fairness to industry, we can table it. And, you know, I mean Europe has been fairly stringent in making sure if the dossier is due in May, they're not going to give them a lot of leeway with the REACH program.

I think we'll probably get the dossier by our September 2013 meeting.

But that begs the question of what to do I mean, that will take care of stearamidopropyl dimethylamine, but what other dimethylamines can we use read across for?

Because the consortium is telling us that you can't use it for the smaller chains. And, again, I can't look at these, Dan, like you, and tell what the C numbers are. But you just told me stearamidopropyl is C18. So are we going to say stearamidopropyl, we'll take care of everything C18 and above? And everything that's C17 and below is going to be "insufficient?"

DR. LIEBLER: Right I can't say that. And I think we can make, perhaps, a more informed we can do better at identifying where we're insufficient once we have the REACH dossier in hand.

DR. BELSITO: But in the meantime, we may be stalling getting asking for data that I mean, I'd rather just go ahead and ask for the data.

DR. BELSITO: that we're not going to get from the REACH dossier.

DR. SNYDER: And not only have the REACH help support what we want to do, or drive our final decision. But we should, I think, go out "insufficient," and ask for the data.

DR. LIEBLER: So, what's the use on cocamido? Is it used?

DR. BELSITO: Yeah, it's nine uses, up to 6.5 percent five in leave ons, four in rinse offs.

DR. LIEBLER: So, cocamido would be nice, because most of these so there are a lot of these ingredients that are derived from fatty oil, you know, a lot of fatty oil mixtures. And so, they all have a distribution of fatty acid chain lengths that almost all of them overlap with the C18, which is the stearamido. But then some of them go down further.

So, cocamido is mostly C12 and C14. It's kind of on the short end of these. So if we were to ask for absorption of the cocamido and, if absorbed, repro and developmental, that actually might satisfy our data need. Between that and the REACH dossier, we might have it covered for this group.

DR. BELSITO: But not sensitization.

DR. LIEBLER: Not sensitization well, you could sensitization on that, too, on the cocamido.

DR. BELSITO: Okay.

DR. LIEBLER: See, cocamido's a nice surrogate for the stuff that's shorter than C18. That's basically what I'm saying. Because it's a mixture of chain lengths that's, you know, C12, C14, and C16 mostly 12 and 14.

DR. BELSITO: Okay. So, can we then keep everything in this document right now, and not suggest that we split it out, and say that for stearamidopropyl dimethylamine, we're tabling further requests for information pending the REACH dossier.

But for the remaining eight ingredients, we would like absorption and, if absorbed, repro toxicity on cocamidopropyl dimethylamine

DR. LIEBLER: Right.

DR. BELSITO: and sensitization and irritation on cocamidopropyl dimethylamine.

And if we don't get those, and if the REACH document satisfied our needs for stearamidopropyl dimethylamine, we'll go with "safe" on the stearamido, and "insufficient" on all the others.

Would that be appropriate?

DR. LIEBLER: Yes.

DR. BELSITO: So that we can at least move the others along, and cut industry a break, and create that little extra reach for stearamidopropyl.

Yes?

DR. SKARE: What about the (inaudible), which is a C22? Where would that fall?

DR. LIEBLER: Longer, I'm not worried about, because there's less absorption, less

DR. SKARE: Yeah, I would agree. I'd just like to make sure I'm

DR. BELSITO: And what about the brassicamido? What's brassica?

SPEAKER: (Inaudible) is 22?

DR. LIEBLER: Yeah, but the brassica the oils what's the chain length on

MS. BURNETT: Uhh they don't have brassica.

DR. LIEBLER: Brassica's not in there?

MS. BURNETT: But, I bet if I go back and look at the

DR. LIEBLER: I'm sure you've got it.

MS. BURNETT: plant oil derived, vegetable oils, I'm sure I've got it there.

DR. ANDERSEN: Well, we actually have HRITT data on the brassica.

DR. LIEBLER: Okay. So palm, we don't have is palm in this one?

MS. BURNETT: Palm is there.

DR. LIEBLER: Oh, it is. Okay. Palm oil is short, it tends to be on the short side for fatty acids, because it's got caprylic, capric, lauric, maristic actually, the most abundant is the lauric, for the palm kernel oil. Oh, palm kernel versus palm. Okay.

MS. BURNETT: And we're looking at palm

DR. LIEBLER: And here we're looking at palmital oh, that's palmitic, never mind. So we don't have palm kernel or palm oil. So, never mind, on that.

I think cocamido probably is our best thing to ask for. It's not showing here, but I looked that up separately.

I think I looked it up in another resource. But cocamido

DR. BELSITO: So, for I mean

DR. SNYDER: You really need to look at this list, because it's more that those nine in that table.

DR. LIEBLER: Right. Yeah. And I've got the list under the "Conclusions."

So, what Don just recapitulated, I agree, too, still.

DR. BELSITO: I mean, for the ones that are larger, I mean, we're not asking for data on them.

So at this point, I think we can say, you know, we're not asking for basically, we can say "insufficient."

What we want is penetration and absorption of the cocamidopropyl and, if absorbed, repro and sensitization and irritation of the cocamidopropyl.

And, by the way, we'll delay re reviewing this document until after May of 2013, when the REACH dossier is expected to come out. So you have nine months, if you don't have this data, to try and generate some of it for us.

And we don't even have to say anything about the stearamido.

DR. LIEBLER: Right.

DR. BELSITO: Okay. (Discussion off the record.)

Oh, rapeseed, brassica. Okay. Yeah. Canola. Yeah. C17, C18. Yeah. Okay. Yeah, they're all basically C18.

(Whereupon, at 3:25 p.m., the PROCEEDINGS were adjourned.)

Marks' Team

DR. MARKS: Okay. Fatty acid amidopropyl dimethylamines. And that's in the Pink Book. In June, the panel issued an insufficient data announcement asking for percutaneous absorption. For example, the shortest chain of fatty acid, lauramidopropyl dimethylamine, and if absorbed, repro and developmental tox. And then sensitization irritation data on oleamidopropyl dimethylamine. We've received nothing to my knowledge. Let me see. What's this, Halyna? Just that we have a memo on August 16th at the REACH Consortium for stearamidopropyl dimethylamine does not support a read across approach. So

DR. EISENMANN: I saw that they're preparing new additional data on stearamidopropyl dimethylamine.

MS. BRESLAWEC: Which won't be ready until March or May 31, 2013. And I think that data would be relevant to this review and will be available next May.

DR. MARKS: And this is on the sensitization?

MS. BRESLAWEC: This includes a range of data, including the developmental and repro.

DR. MARKS: And do you think, Rons, that if we have development and repro on stearamidopropyl that that will be able to be a read across for the other ones?

DR. HILL: I think we still had the concern about the shortest chain ones in terms of their ability to penetrate to a greater extent than some of these larger ones. And my comment was given the complete lack of any biochemical effect data of any kind for these, what we should get from the REACH report would be really helpful. I think it might still limit the read across to some of the shortest chain ones where we don't have in the absence of dermal penetration data, which we understood would likely not be forthcoming because either very small amount of use or no use.

MS. BRESLAWEC: Yeah, we are not the data on lauramidopropyl dimethylamine will not be forthcoming.

DR. EISENMANN: Not that we're aware of.

DR. HILL: That was my expectation.

DR. EISENMANN: I think most of the industry is acknowledging that it's a sensitizer, so they're not going to be developing more data.

DR. HILL: I'm wondering if that's also true of myristoyl, which is, I think C 14, isn't it? So.

DR. EISENMANN: I think they're basically looking at 16 and above because the stearamide is a mixture of 16 and 18. So they're looking at that and above and not anything smaller.

DR. HILL: So then we need to go back to the amino acid compositions in my estimation and see what we might could read across. And they're saying they don't support read across if I understood correctly.

DR. EISENMANN: For below.

DR. BERGFELD: Is it possible that such a statement could be sent to us, the status of their review and why they would not be looking at the lower PEGs so that we could use that as a document?

DR. EISENMANN: I did send statements.

DR. MARKS: So how would you like to proceed? Should we move

MS. BRESLAWEC: It was an August 16th statement.

DR. BERGFELD: I had it somewhere. I guess I didn't put it in my book.

DR. HILL: I think that came in Wave 2, didn't it?

DR. BERGFELD: You could table it until you have the other information that's been promised but also without the understanding that you will relate to the statement of sensitization and state that it would not be considered safe under this PEG 18. Is that what it would be? 16/18?

DR. EISENMANN: Well, you have to remember that these are it would be nice to have a conclusion that they're safe at the contaminant levels of (inaudible). That's probably the level we'd like.

DR. BERGFELD: So you could use that in your discussion.

MS. BRESLAWEC: Yeah, but we feel it would be appropriate to table this discussion until the REACH data are available.

DR. MARKS: Rons, Tom, is that that was not one of the potential conclusions I had for this table. But

DR. HILL: I would say that would certainly be my preference just, like I say, based on the absence of any biochemical effects data of any of these. If we get at least indirect assessment of that through this information, that would be, for me, extremely helpful because I haven't been comfortable with these amidoamines since way back when we were looking at cocamidopropyl betaine.

DR. MARKS: So with those, as you recall, sensitization was the most concerning.

DR. HILL: Everybody but me..

DR. MARKS: Okay. And it was red flagged. We were actually, as a team, were going to move forward with it safe. We didn't have the repro and the development issues as I recall. But

DR. HILL: I'm thinking that was true for everybody but me in the last meeting, and I don't recall whether I abstained from the vote, which might have been what I did in the full day meeting.

DR. MARKS: No, I think it was actually Dan who raised the issue of getting those if absorbed, getting that data again for the shortest chain fatty acid.

DR. HILL: But I also wanted to see it. I was happy that he mentioned it and it wasn't me that was the problem child that day.

DR. MARKS: So table is what I hear. And I will be making the motion tomorrow, awaiting am I referring to his correctly, the REACH data?

MS. BRESLAWEC: Right, which is due end of May next year.

DR. ANDERSEN: I think, Jim, a question that I would have is how are we going to get the REACH data? Is that something that the Council will be in a position to provide or are we going to have to get it ourselves?

DR. EISENMANN: I'll keep working with the company that belongs to the consortium. They've already provided some data in the report, so I will

DR. ANDERSEN: Fingers crossed.

DR. EISENMANN: Right.

MS. BRESLAWEC: Keeping in mind that the REACH data that is generated by a consortium, and so the best we can often get for that is a summary. And since Carol is working directly with one of the companies that's providing the data, we may be able to do something better.

DR. EISENMANN: And they provided most of the data a lot of the data that's in the report already that's in the format of three summaries.

DR. MARKS: And again, did you say that it's just going to really be focused on the stearamidopropyl?

DR. EISENMANN: Correct. That's all this consortium

DR. MARKS: That's all. So we get this next spring. Are we going to be able to move forward with a conclusion or are we still going to have more data needs that this is not going to be maybe we'll be able to say more about stearamidopropyl dimethylamine, but my concern was the oleamidopropyl because we have the case reports and we don't have RIPT.

MS. BRESLAWEC: Well, those are sensitizers.

DR. MARKS: Yes. Well, but we can't determine a level at this point, I think, to go forward and say it's safe at this level. Unless we take the tact that we did with the cocamidopropyl betaines is it's safe when formulated to be nonsensitizing. And that is what we were going to do the last meeting when we were going to move forward with a safe conclusion as long as formulated to be nonsensitizing. So that doesn't allay our fears, Ron Hill.

DR. HILL: I think it does because when you drop it down to a level where that's not an issue, that essentially serves as a sentinel, I mean, that's how I resolve the issue in my mind when we looked at cocamidopropyl betaine, that if you got the levels down to where we didn't see a significant incidence of sensitization, then any of the other biological concerns basically go away in my mind at least.

DR. MARKS: So you're okay with the repro and the developmental. Obviously, Ron Shank was before it was Dan who brought up the issue on the other team. Or the other team brought up the issue of the repro and developmental toxicity. So I'm going to backtrack a little bit and say are we going to table it awaiting the REACH data? Is that going to really change much of anything?

DR. HILL: I mean, I was very comfortable with the discussion section as it was written. I opened this report with a great deal of apprehension, but once I read the discussion as it's written I was very happy with it. What it doesn't provide is a loophole if there are data that supports a little higher concentrations, for example, that come out of the REACH studies. But I don't know, I guess you could reopen at that point, right? And amend the conclusion if we do that sort of thing, don't we?

DR. ANDERSEN: Yes.

DR. HILL: Are there negative impacts in the meanwhile, I mean, given that timeframe? And you guys can answer that better than me..

DR. MARKS: Well, in that case we're back to a conclusion of insufficient. So we've had requests from

DR. ANDERSEN: Insufficient for the shorter chain ones.

DR. SLAGA: Right. That's what the insufficient is for.

DR. ANDERSEN: Not for the entire group.

MS. BRESLAWEC: And we don't expect to be able to provide that data.

DR. EISENMANN: Right.

DR. BERGFELD: But I don't understand why you couldn't handle that in your discussion. They've already said it's a sensitizer. They've given you a document you can reference. So you could handle that in your discussion and even in your conclusion.

DR. EISENMANN: So would you change the conclusion for safe as used for the stearamidopropyl and then safe and larger and insufficient for amidopropyl?

DR. MARKS: So we need to be specific as to exactly where are we going to make that cutoff? Insufficient for the shorter chain. So what chain length is that going to be? Obviously, the prototype we were going to use was the lauramidopropyl, but

DR. HILL: Part of the significance of that was because we have some that are natural oil based. So I don't remember from our fatty acid review which ones had the greatest I was trying to pull an example that would have the greatest percentage of shorter chain fatty acids and I can't my memory is simply not that good.

MS. BURNETT: If you want to look at page 97 in the Panel Book.

DR. HILL: You have that in there. All right.

MS. BURNETT: Fatty acid composition.

DR. HILL: Yeah, I knew that was here. I guess what I'm saying is I didn't look before I opened my mouth to speak just then. The point being that some of them will have smaller quantities of the shorter chain fatty acids, and then we have to decide. But then again, if the whole ingredient is there at 0.5 percent, let's say, then the maximum amount of this one would be 0.02 percent or whatever that happens to be. So, 97 you say?

MS. BURNETT: 97.

DR. HILL: So if you look at Babassu, there are quite a few shorter chains in there. But most of the others, palm kernel, same deal. Most of the others it's C16 and up. And the larger quantities of the long chain ones. However, that is where I was saying if you require formulated to be nonsensitizing, that means somebody has to do those studies, right? And then to me that's sentinel because if they keep it at levels below where we see sensitization, probably none of that other biology is going to be of any concern. Highly likely none of that other biology would be of any concern, so that was my mindset. These ones where there are larger amounts, considerably larger amounts of even C8 fatty acids, I don't know. That makes me less comfortable.

DR. MARKS: So with that in mind we could, again, the conclusion could be safe to be present use in concentration when formulated to be nonsensitizing. And then for the shorter chain ones, which one are we going to pick out as being insufficient?

DR. HILL: Even, this is there were, you know, it would be awfully nice to have data but it's not going to, you know, even there I'm thinking if you formulate it to be nonsensitizing, the amounts that we'd be talking about I'd be curious to see what Dan would think on this, but anybody on the other panel, it's likely we're going to develop the kinds of concentrations one would need to see significant repro tox effects. I'm going on thin air at a level.

DR. MARKS: So I would still raise the concern about oleamidopropyl dimethylamine, although, again, when you do formulate it to be nonsensitizing, it's below my concern. You know, it's not going to be sensitizing. So that's where we were the last meeting. Our team felt that we could find these ingredients to be safe as long as formulated

to be nonsensitizing. Ron Shank and Ron Hill, you were concerned about the repro and the developmental toxicity. So shall I move tomorrow that rather than table, that we move with a safe conclusion? And we can see how it runs again tomorrow. See whether we have a run and then Ron Hill, you and Dan can have a discussion.

DR. HILL: And anybody else who wants to chime in, by the way.

DR. MARKS: Yeah. So we'll see whether the other team's changed. So I'm going to move tomorrow that it's safe, nonsensitizing. And then we'll see what occurs.

So it seems like our team then is not going to await the REACH data. We don't think that will change our conclusion, so we don't think it needs to be tabled. Pardon?

DR. SLAGA: It still would be insufficient.

DR. MARKS: Yeah. Okay. Safe to be nonsensitizing. So we would move that there would be a tentative report on the fatty acid amino propyl dimethylamines with a conclusion that it is safe as long as formulated to be nonsensitizing. Safe in the present practices and use and concentration if they were being used, et cetera.

Any other comments? Ron? The two Rons? This is a rerun for us. At least we're consistent.

Okay. We'll see what happens tomorrow. It should make for an interesting discussion.

DR. SHANK: In the discussion I would like to change the word "trepidation." I don't think the panel really expressed any fear.

DR. HILL: I did.

DR. SHANK: Did fear, okay.

DR. HILL: I did.

DR. SHANK: Perhaps the CIR

DR. HILL: But you can remove it. It seems silly.

DR. SHANK: Expressed concern..

DR. HILL: It seems silly to use that word.

DR. SHANK: I like the colorful language.

MS. BURNETT: I think that's going for another adjective or whatever.

DR. HILL: Something other than concern?

MS. BURNETT: They had been writing concern in several spots and I was just

DR. SHANK: Yeah, just wanted to spice it up?

MS. BURNETT: Yeah.

DR. HILL: I liked it but at the same token I agree that it probably needs to go.

DR. MARKS: Ad obviously, the discussion will delete that last that paragraph about insufficient and the data needs.

Christina, thank you.

DR. BERGFELD: Do you want to add there that if present that the PEG 18 and under could be sensitizing? I mean, you already have there that the North America Contact Dermatitis Group test panels added one of these ingredients.

DR. MARKS: Yeah, that was oleamidopropyl dimethylamine. And I want my initial request was to see an RIPT because as I recall it was sensitizing in a let me see allergic contact dermatitis had been reported at levels of 0.03 percent and the use concentration in cosmetics is up to 1 percent. But, if we're formulating it to be nonsensitizing then it'll be inherent on the industry to have it a low enough concentration that that's not going to be an issue. Presumably, it's going to be something significantly less than 0.3 percent, so that use concentration will be lower probably, unless they have data that suggests that 1 percent in that particular formulation is nonsensitizing.

Rachel, did you have no? Okay. Comments. We know you'll have some comments about our next ingredient so I'm looking forward to that discussion.

Any other comments about this? I will issue I will move that we issue a tentative report with a conclusion safe as long as formulated to be nonsensitizing. The discussion, Christina, will obviously include the comments about oleamidopropyl dimethylamine.

Full Panel Meeting

DR. BERGFELD: Now we're going to go to the reports going to the next level, and the first one there is Dr. Marks and the fatty acid amidopropyl dimethylamines.

DR. MARKS: I suspect this ingredient is going to these ingredients are going to elicit another discussion. So, in June the CIR Expert Panel issued an insufficient data announcement. One, getting percutaneous absorption of the shortest chain fatty acid. For example, the lauramidylpropyl dimethylamine. And if absorbed, repro and development toxicity. And also, we wanted sensitization/irritation data.

We've not received this data. However, our team went back and looked at our handling of these ingredients back in June and we actually felt that we could issue a safe as long as it was formulated to be non sensitizing. That would take care of the issue with the oleamidopropyl dimethylamine, and so we would move that we issue a tentative report on the fatty acid amidopropyl dimethylamines with a conclusion of safe as long as formulated to be non sensitizing.

And I'll let we'll see whether we get a second of that, but I'll let Ron Shank discuss and Ron Hill, if he wants, the issue of repro and developmental toxicity and why we were not concerned about that.

DR. BERGFELD: Ron Shank, then Ron Hill.

DR. MARKS: While Ron's looking for that, I'll mention we had considered tabling this until we received the REACH data on the stearamidopropyl. But we felt even with that data it really wouldn't impact our decision.

DR. BERGFELD: I'll let Don speak and then we'll wait for Ron to get to the place he needs to be.

DR. SHANK: Thank you.

DR. BELSITO: Well, you know, we also considered the memo that we got from Halyna regarding the fact that the REACH dossier was expected on stearamidopropyl dimethylamine by May of 2013. But we also considered very strongly the fact that the consortium putting that dossier together advised us that the read across approach for these other akyl amidopropyl dimethylamines is not appropriate because the shorter chains would penetrate and perhaps have a higher sensitization potential.

So, we actually wanted to go insufficient and we changed the ingredient that we wanted. We wanted absorption of cocamidopropyl dimethylamine, and if absorbed, reproductive toxicity studies, and we wanted sensitizaiton and irritation on that.

Putting out this insufficient, however, we also wanted to let industry know that we would not bring this back until after May of 2013, so that we could also see the information in the REACH dossier. But we wanted to proceed letting them know that even with the information for the stearamido, we would still have concerns for the smaller size.

DR. BERGFELD: Ron, are you ready? Ron Shank?

DR. SHANK: Yes. It was just the use concentrations are quite low in leave-on products, and this would not present a toxicological concern. (Laughter)

DR. LIEBLER: I just want to go on the record saying that I'm loving this. (Laughter)

DR. BERGFELD: Ron Hill?

DR. MARKS: Ron Shank, will you rephrase that to below the level of toxicologic concern?

DR. SHANK: No. Below a concern for reproductive and developmental toxicity. That specific. (Laughter)

DR. BERGFELD: Okay.

DR. BELSITO: Well, the cocamidopropyl is 6.5 in dermal contact.

DR. SHANK: That's in a rinse off?

DR. BELSITO: No, dermal contact, read across, white bar.

DR. SHANK: Which one?

DR. BELSITO: Cocamidopropyl dimethylamine, the one we asked for data on.

DR. SHANK: In my book it says that's in a rinse-off.

DR. BELSITO: Mine says exposure type dermal contact.

DR. SHANK: Well, dermal contact can be from a rinse-off. But in the leave-ons, it's

DR. BELSITO: Okay, 0.03. You're right, sorry. Mea cupla.

DR. BERGFELD: Would that change your opinion, Don, with what you're requesting?

DR. BELSITO: You know, I'm not the repro toxicologist. It would still not change my opinion about the need for sensitization and irritation, whether it would change my need for absorption I'm not in a position to answer.

I mean, basically what the consortium who is putting this stearamidopropyl is telling us we cannot read across their data to the other one. So from the standpoint of sensitization and irritation, I'm not satisfied that we can go safe as used.

DR. MARKS: That's why we put formulated to be non sensitizing. And actually, it wasn't the lower one, it was the as in the minutes. The oleamidopropyl diethylamine I was most concerned about because we have actual case reports with a concentration, with positive patch tests, and that's actually been alerted to us in the North American group that has added it to our patch test screening. So, that was the one I was concerned with and that's why we put on there safe to be non sensitizing, to address that issue of irritation and sensitization.

DR. BERGFELD: Ron Hill?

DR. HILL: Yeah. I mean, I think what we talked about yesterday, I don't remember that I had anything to add, but what I'd said was if you mandate that it's formulated to be non sensitizing then the odds of formulating in a leave-on at a high enough concentration that it would cause any reprotox effects are highly unlikely. So we're basically using the sensitization as a sentinel, if you will, for any other potential effects like that. That we would be by mandating non sensitization to get to the levels where you could reasonably expect any kind of repro tox would certainly, I think, certainly see high levels of sensitization and you wouldn't formulate to that concentration. So it was a sentinel indicator is how I looked at it. I don't know if there's precedent for that or not, but that's the way I was that is the mindset we had when we looked at this as an impurity in cocamidopropyl betaine.

DR. BERGFELD: Don, then Curt.

DR. BELSITO: I mean, if you objected to TTC for impurities, then I have to strongly object to below the level of sensitization.

I think irritation is one thing because irritation is dependent upon so many factors. You know, pH, what else is in there, yadda, yadda, yadda. But sensitization is sensitization, and we have no data on this. And you know, when we dealt with cocamidopropyl betaine, it was the impurity. So again, it was a TTC approach to these sensitizing impurity.

Now, we're using a TTC approach to the actual chemical, and I strongly object to that. That is not the use of TTC.

DR. LIEBLER: In view of the fact that we can expect this REACH dossier, which is I think going to be a very helpful document, we know it's coming. And so, you know, I strongly support the idea of tabling this until that material arrives, and also to take advantage of the intervening time to ask about cocamido because cocamido has the advantage of providing us data on C12, C14, and some C16. And, it's used whereas the lauramido which we specified previously is I don't think it's used or it's a sensitizer so it's we're not going to get data on that, as Jay pointed out to us in our discussion.

So, cocamido we're more likely to get data and I think if we given that the REACH dossier is coming, there's time to generate some data on the cocamido. There are uses, so there would be some incentive. Then, we would actually have a nice package to make a decision on and not have to be in this mode of trying to use a threshold of toxicological concern rationale for an ingredient as opposed to an impurity.

DR. MARKS: I will withdraw my motion, and the only thing I would like to add is the insufficient. I would like to include to get an RIPT on the oleamidopropyl dimethylamine.

DR. BERGFELD: I'm sorry, are you withdrawing to table or insufficient?

DR. MARKS: No, I think I move that it be safe as long as formulating to be non sensitizing, and

DR. BERGFELD: You would do that?

DR. MARKS: Well, now I withdraw it. We were having this discussion. Don, if you want to propose your motion I would support the insufficient data announcement but I would also besides the request of data you mentioned, include an RIPT on a oleamidopropyl dimethylamine.

DR. BELSITO: Actually, yeah. I mean, looking at that I would have no problem. Actually, Dan, when you look and as Ron pointed out, I incorrectly read across and thought 6.5 was a leave on because of the dermal contact. It's a wash off. The leave-on for cocamidopropyl is 0.003, so I would actually like to see this sensitization and irritation on the oleamidopropyl dimethylamie, and perhaps the penetration on the cocamidopropyl dimethylamine, or the absorption, rather. Enough absorbed, then repro toxicicity. Go ahead not with a table but with an insufficient, but with the agreement that we'll wait for the dossier from REACH before bringing it back to the panel. But at least so industry is on alert, that we don't think the dossier is going to answer all our questions, particularly since the consortium has told us that we can't read across from that dossier.

DR. BERGFELD: Halyna?

MS. BRESLAWEC: We simply have no issue with tabling it, that was our proposal.

DR. BELSITO: We're not tabling it.

MS. BRESLAWEC: No, I'm sorry. With waiting for the REACH data.

DR. BELSITO: Right.

MS. BRESLAWEC: For that. With regard to the additional insufficient information on the cocamidopropyl dimethylamine, I want to point out that there are nine uses of that. So, we will go back to the manufacturer that does use this and ask for additional data. The Council as a whole will not be generating additional data to support that insufficient.

I would also like to ask Carol to talk about some data that are already in the report.

DR. EISENMANN: I don't know if you saw that there was a summary from the CAPB report in there that includes some data in that summary on dimethylamine, which is the cocoa

MS. BRESLAWEC: Cocoa?

DR. EISENMANN: Right, and in that report we were calling it amidoamine. So I'd ask you to look to add those studies to the table, so you have all the studies on these ingredients in one spot. So, you may have missed there's a few more sensitization studies in that discussion on those ingredients themselves now.

MS. BRESLAWEC: While they were in the original part, they just haven't been highlighted so it was easy to miss it.

DR. BELSITO: And you know, before, you know, requested things and then we looked at greater detail from other studies have decided that they weren't

DR. BERGFELD: Helpful? Paul?

DR. SNYDER: Yeah, we also noted that this report has no absorption, distribution, secretion data and no tox data, as compared to the CAPB report which didn't have absorption, distribution in the data but it had lots of tox data. So, we that's why we still are going along the lines that we want absorption and the other information that we requested in the insufficiency.

DR. BERGFELD: So, Ron Hill?

DR. HILL: I was just going to add the reason that I thought the sensitization would serve as a reasonable sentinel here is because at least yes, we don't know with certainty, but highly likely metabolism of the amine generates an aldehyde which leads to heptin generation, and that would be the mechanism most likely for sensitization, and to get above those levels where you weren't seeing sensitization enough systemically to have a possibility of repro tox, which of course I'm always worried about. It seems to be highly unlikely, so I didn't just dream this up in my mind, there's rationale that went with it.

DR. BERGFELD: So we have a motion, and I think it's been seconded to make it insufficient data announcement. We have a list that's been generated; I wonder if you have the list?

DR. ANDERSEN: My problem is that we're well past that.

DR. BERGFELD: Oh, we are?

DR. ANDERSEN: We previously had issued an insufficient data announcement. It's time now to issue a tentative report. And

DR. BELSITO: So then I think we have no other option to table it, because I think we should wait for the dossier but industry should be on alert that when we get the dossier it's possible that the only ingredient that will be approved as safe will be the stearamidopropyl.

DR. BERGFELD: So, we need a motion to table? That's your motion? A second?

DR. BELSITO: I'll make the motion.

DR. MARKS: Second.

DR. BERGFELD: There's no discussion on the table a motion. All those in favor of tabling?

MS. BRESLAWEC: Excuse me, is the stearamido and larger or just stearamido?

DR. BELSITO: I think, we'll probably feel the larger ones are okay. I mean, the data we're asking for are on the smaller ones.

DR. BERGFELD: So, there's no discussion, again on a tabled motion. All those in favor of tabling, please indicate. So, this ingredient has been tabled awaiting the REACH data. And a special request I think we should go through the special request as Alan understands it.

DR. ANDERSEN: I think there were two areas of information. One is we've retained the request for sensitization/irritation data on oleamidopropyl dimethylamine, and we'll take another look at Carol's suggestion that in fact maybe there are actually more data on that than needed. And then we added the cocamidopropyl dimethylamine per cutaneous absorption.

DR. BERGFELD: Okay, alright. Thank you. We'll move on, then, to the next ingredient which is the PEGylated oils.

DR. SHANK: These are mixtures? So, how do you do absorption on the mixture?

DR. LIEBLER: It's an ingredient

DR. SHANK: Technically, how do you do that?

DR. LIEBLER: You mean the cocamidopropyl?

DR. SHANK: Yes. Is that not a mixture?

DR. HILL: It is a mixture.

DR. LIEBLER: Yeah.

DR. SHANK: So, how do you do the absorption? Technically, how is that done?

DR. LIEBLER: So, what you could do is you could use LCMS to measure the C12 and C14, which are the two major fatty acyl version constituents of that mixture, and those would be representative of the penetration of the mixture. You could go to C16, and I don't think there's anything much below C12, but I mean that's a pretty straightforward assay these days.

Safety Assessment of Fatty Acid Amidopropyl Dimethylamines as Used in Cosmetics

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The 2014 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 Lillian J. Gill, DPA. This safety assessment was prepared by Christina Burnett, Scientific Analyst/Writer, and Bart Heldreth, Ph.D., Chemist CIR.

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DRAFT ABSTRACT

The Cosmetic Ingredient Review Expert Panel reviewed the safety of fatty acid amidopropyl dimethylamines, which function primarily as antistatic agents in cosmetic products. The Panel reviewed relevant animal and human data related to these ingredients and determined that additional data are needed: (1) percutaneous absorption of the ingredient that has the shortest chain fatty acids (e.g., lauramidopropyl dimethylamine), and if it is absorbed; (2) reproduction and developmental toxicity data; and (3) sensitization an irritation data on oleamidopropyl dimethylamine at use concentration. The Panel concluded the data are insufficient to support the safety of these cosmetic ingredients.

INTRODUCTION

The fatty acid amidopropyl dimethylamines function primarily as antistatic agents in cosmetic products. These chemicals are sometimes referred to as "amidoamines". The full list of ingredients in this safety assessment is found in Table 1.

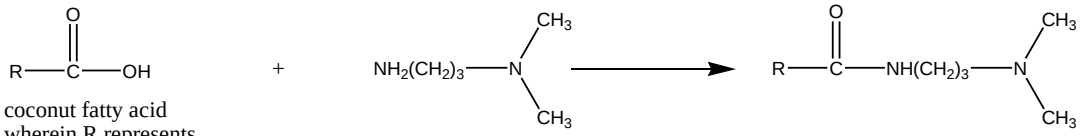
In December 2010, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) issued a final amended safety assessment on cocamidopropyl betaine (CAPB) and related fatty acid amidopropyl betaines.[1] The Panel concluded that these ingredients "were safe in cosmetics as long as they are formulated to be non-sensitizing, which may be based on a quantitative risk assessment." The Panel had expressed great concern related to the impurities that may exist in the amidopropyl betaines because of their sensitizing potential. Those impurities were 3,3-dimethylaminopropylamine (DMAPA) and the fatty acid amidopropyl dimethylamines presented as ingredients in this report. A quantitative risk assessment (QRA) on DMAPA at a concentration of 0.01% in raw CAPB indicated no sensitization in finished cosmetic products; amidoamine at a concentration of 0.5% in raw CAPB may cause sensitization in certain finished cosmetic products. The Panel advised industry to continue minimizing the concentrations of the sensitizing impurities. The summaries of the studies on DMAPA and amidoamine that the Panel reviewed in the CAPB safety assessment have been incorporated into this safety assessment.

Toxicological data on stearamidopropyl dimethylamine (synonym: N-[3-(dimethylamino)propyl] stearamide) in this safety assessment were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by private companies as part of the REACH chemical registration process. These data are available on the ECHA website.[2]

CHEMISTRY

The definitions and CAS registry numbers, where available, of the fatty acid amidopropyl dimethylamines ingredients are presented in Table 1. The structures of these ingredients and available information on the physical and chemical properties of these ingredients are presented in Figure 2 and Table 2, respectively.

The ingredients in this review each have the same core structure of a fatty acid amide, *N*-substituted with 3-propyl-*N'*,*N'*-dimethylamine. These ingredients are manufactured by the amidation (i.e., amide-forming condensation) of fatty acids with 3,3-dimethylaminopropylamine (DMAPA), most commonly under alkaline or acidic conditions (Figure 1).[3,4] The resultant ingredients have an identical core, with two primary functional groups, a secondary amide and a tertiary amine, separated by a propyl chain. These ingredients only differ by the identity of the fatty acid chain(s) attached to the amide functional group of this core. The synthesis of these ingredients is a clean process with little to no by-products, and typically yields products that are 98-99% pure fatty acid amidopropyl dimethylamines.[5] Accordingly, starting materials, such as DMAPA, represent the largest concern for impurities.



coconut fatty acid wherein R represents the various fatty acid chain lengths derived from coconut oil

3,3-dimethylaminopropylamine (DMAPA)

cocamidopropyl dimethylamine (an amidoamine)

Figure 1. Synthesis of Cocamidopropyl Dimethylamine

Despite the long alkyl chain substituents therein, these ingredients are readily solubilized in water, as they are easily converted into ammonium salts (i.e., cationic surfactants) at even mildly acidic pH values (i.e., the tertiary amines are protonated to ammonium cations; these ingredients are alkaline materials with pK_b values in the range of

5-6).[4,5] Due to their high polarity, both as the free tertiary amines and as the ammonium salts formed in-situ, these ingredients perform excellently at dissipating triboelectric charges (i.e., static electricity), even at low concentrations (e.g., 0.1% w/w).[5-7] This property likely accounts for the claimed functions of these ingredients as antistatic agents and, at least in part, as conditioning agents. Although not formally claimed, these ingredients are also known to operate as functional surfactants, thickeners, and bacteriostatic agents.[5]

Method of Manufacturing

Cocamidopropyl Dimethylamine

According to a supplier, cocoamidopropyl dimethylamine is made by mixing together refined coconut oil with DMAPA and heating the mixture to > 75 ^{o}C and < 175 ^{o}C.[8] The progress of the reaction is followed using standard analytical tests until specifications are met. The product is then filtered and stored in lined steel drums.

N-Nitrosation and Safety Issues

Although nitrosamine content has not been reported, fatty acid amidopropyl dimethylamines are composed of secondary amides and tertiary amines, and potentially can be nitrosated. Of the approximately 209 nitrosamines tested, 85% have been shown to produce cancer in laboratory animals.[9] Nitrosation can occur under physiologic conditions.[3] Depending on the nitrosating agent and the substrate, nitrosation can occur under acidic, neutral, or alkaline conditions. Atmospheric NO_2 may also participate in the nitrosation of amines in aqueous solution.[4] Accordingly, fatty acid amidopropyl dimethylamines should be formulated to avoid the formation of nitrosamines.

Impurities

Behenamidopropyl Dimethylamine

A supplier has indicated that the maximum level of DMAPA in behenamidopropyl dimethylamine is 115 ppm.[10] The supplier stated that the typical use level of this material in hair conditioners is 2.3%, which results in a maximum DMAPA level of 2.65 ppm in the finished product.

Cocamidopropyl Dimethylamine

A supplier reported the final composition of the product cocamidopropyl dimethylamine to be 83-90% cocamidopropyl dimethylamine, 8.9-9.4% glycerin, 1.0% (max) DMAPA, and 5.0% (max) glyceryl esters.[8]

Oleamidopropyl Dimethylamine

A product description sheet indicates that oleamidopropyl dimethylamine is at minimum 88% pure and has a maximum concentration of 0.60% DMAPA.[11]

Stearamidopropyl Dimethylamine

The maximum level of DMAPA in stearamidopropyl dimethylamine has been reported to be 30 ppm.[12] The supplier stated that, in the typical use concentration of 2.14% stearamidopropyl dimethylamine in hair conditioners, the DMAPA level in the finished product is a maximum of 0.65 ppm. Another supplier indicated that the free DMAPA in stearamidopropyl dimethylamine is less than 0.2%.[13]

In another sample of stearamidopropyl dimethylamine, the chemical composition was at minimum 97% of the active matter and contained at maximum 0.002% free DMAPA and 3.0% free fatty acid.[14] The C-chain distribution for this sample of stearamidopropyl dimethylamine was reported as the following: <C16 = <1%; C16=<5%; C18 = >93%; and >C18 = <1%.

Finally, a sample of stearamidopropyl dimethylamine was determined to have < 20 ppm residual DMAPA, < 1ppm secondary amines, and <50 ppb nitrosamines.[15]

USE

Cosmetic

All but one of the 24 fatty acid amidopropyl dimethylamines included in this safety assessment function as antistatic agents in cosmetic formulations.[16] Brassicamidopropyl dimethylamine is reported to function as hair and skin conditioning agents. In addition to being an antistatic agent, stearamidopropyl dimethylamine is reported to function as a hair conditioning agent.

Table 3 presents the frequency and maximum use concentration ranges for fatty acid amidopropyl dimethylamines. According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), stearamidopropyl dimethylamine has the most reported

uses in cosmetic and personal care products, with a total of 427; 355 of those uses are in rinse-off formulations.[17] Most of the rinse-off uses are in hair conditioners. Behenamidopropyl dimethylamine has the second greatest number of overall uses reported, with a total of 35; 32 of those uses are in rinse-off formulations. Again, most of the rinse-off uses are in hair conditioners. A few uses were reported each for brassicamidopropyl dimethylamine (1); cocamidopropyl dimethylamine (6); isostearamidopropyl dimethylamine (13); lauramidopropyl dimethylamine (1); minkamidopropyl dimethylamine (1); oleamidopropyl dimethylamine (12); and palmitamidopropyl dimethylamine (1). No uses were reported to the VCRP for the remaining fatty acid amidopropyl dimethylamines.

In a survey of use concentrations conducted by the Personal Care Products Council, stearamidopropyl dimethylamine is reported to be used at a range of maximum concentrations of 0.01%-5%, with 5% reported in non-coloring hair conditioners.[18] In behenamidopropyl dimethylamine, the range of maximum concentrations was reported to be 0.3%-3%, with 3% reported in non-coloring hair conditioners. A range of maximum concentrations for cocamidopropyl dimethylamine was reported to be 0.003%-6.5%, with 6.5% reported in skin cleansing products. No use concentrations were reported for almondamidopropyl dimethylamine; avocadoamidopropyl dimethylamine; babassuamidopropyl dimethylamine; minkamidopropyl dimethylamine; oatamidopropyl dimethylamine; oliveamidopropyl dimethylamine; sesamidopropyl dimethylamine; tallamidopropyl dimethylamine.[19]

Oleamidopropyl dimethylamine and stearamidopropyl dimethylamine were reported to be used in cologne, indoor tanning products, and other propellant and pump spray products, and could possibly be inhaled. Oleamidopropyl dimethylamine and stearamidopropyl dimethylamine were reportedly used at concentrations up to 0.15% and 2%, respectively, in these spray products. 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 below 10 µm compared with pump sprays.[20,21] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[22,23]

The amidoamine ingredients in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[24]

Non-Cosmetic

Myristamidopropyl dimethylamine is used as a biocide in contact lens disinfecting solution (concentration reported to be ~0.0005%) and may have uses as a broad-spectrum therapeutic antimicrobial for keratitis and for surgical prophylaxis.[25-30]

TOXICOKINETICS

Absorption, Distribution, Metabolism, Excretion

In an IH Skin Perm QSAR model, the dermal absorption of stearamidopropyl dimethylamine has been estimated to be 0.04 mg and 0.12 mg after 8 and 24 h, respectively, with absorbed fractions being 0% at each time period.[2] The maximum dermal absorption rate was calculated to be 2.40×10^{-6} mg/cm^2/h. The calculations were based on an instantaneous deposition dose of 9257 mg and a skin area of 2000 cm^2.

No other studies were found on the absorption, distribution, metabolism, and excretion of fatty acid amidopropyl dimethylamines.

TOXICOLOGICAL STUDIES

Acute Toxicity

Oral – Non-Human

Stearamidopropyl Dimethylamine

The acute oral toxicity of 10% (w/w) stearamidopropyl dimethylamine in propylene glycol was tested in 6 female Wistar rats.[2] The rats received 2 dosages of 1000 mg/kg body weight of the test material within 24 h. The rats were observed daily for clinical signs of toxicity for 14 days. Two of the 6 animals died on day 2 and day 3, respectively. Clinical signs observed of both the animals found dead and the surviving animals included hunched posture, lethargy, uncoordinated movements, piloerection, diarrhea, chromodacryorrhea, pallor, and/or ptosis. Recovery from these symptoms in the surviving animals occurred between days 7 and 10. The 2 animals that died during observation had either slight weight gain or weight loss. Three of the 4 surviving animals had body weight loss between days 1 and 8, but gained body weight between days 8 and the end of the observation period. In one dead animal, necropsy showed watery-turbid fluid in the stomach and watery-clear, yellowish fluid in the small intestine. The other dead animal had a spleen of reduced size. In the surviving animals, one rat had pelvic dilation

of the kidneys. No other abnormalities were observed in the remaining animals. The oral LD_{50} for stearamidopropyl dimethylamine in this study was determined to be greater than 2000 mg/kg body weight.

In another oral toxicity study, 40% (w/w) stearamidopropyl dimethylamine in deionized water was tested in 20 male and 20 female Sprague-Dawley rats.[2] Dose levels were 420, 1990, 3910 and 5470 mg/kg body weight and were delivered in dose volumes of 1.67, 2.21, 4.44 and 6.22 mL/kg body weight, respectively. Post treatment, animals were observed for clinical signs and mortality at 1/2, 2 and 4 h and then daily up to 14 days. No mortalities were observed in the 420 and 1990 mg/kg dose groups. Two males and 4 females in the 3910 mg/kg dose group and all rats in the 5470 mg/kg dose group died during the observation period and within 8 days of administration of the test material. Clinical signs observed included diarrhea, soft stool, brown stained abdomen, anal or urogenital region, hypoactivity, hypersensitivity to touch, red stained nose and mouth, hair loss on abdomen and hindquarters, ataxia, emaciation, bloated abdomen, red stain around eyes, piloerection, lacrimation, high carriage, dyspnea, and hypothermia to touch. At necropsy of the animals that died during the observation period, reddened mucosa was observed in 3 animals from 3910 mg/kg dose group and 1 animal from 5470 mg/kg dose group. No other treatment-related changes were reported for any animals in this study. The oral LD_{50} for stearamidopropyl dimethylamine in this study was determined to be 1396 mg/kg body weight.

Repeated Dose Toxicity

Oral – Non-Human

Stearamidopropyl Dimethylamine

In an oral 14 day dose range finding study performed in accordance to OECD guideline 407, stearamidopropyl dimethylamine in propylene glycol (concentration not reported) was administered to 3 Crl:WI(Han) rats/sex/dose via gavage at dose levels of 0, 50, 200 and 500 mg/kg body weight/day.[2] No mortalities were observed during the treatment period in the low and mid-dose groups. All animals in the 200 mg/kg/day dose group were observed with piloerection on 2 days during the second week only. No clinical signs of toxicity were observed in the low dose group. Body weights, body weight gains, and feed consumption were comparable to controls. Hematological changes in the low and mid-dose groups consisted of slightly lower red blood cell and higher reticulocyte counts in males. No dose-related trend was noted with these changes. Clinical biochemistry changes consisted of higher alanine aminotransferase activity in two males in the low dose group and two males and one female in the mid-dose group, higher alkaline phosphatase activity in one female in the mid-dose group, and higher potassium levels

in males in the low and mid-dose groups. No abnormalties or histopathological changes were noted at necropsy of the low and mid-dose groups. Slight increases in spleen and thymus weights of the mid-dose group females were comparable to the control group.

All animals in the high dose group were killed for humane reasons between days 6 and 8. From day 4 of treatment and after, these animals were observed with lethargy, hunched posture, labored respiration, abdominal swelling, piloerection, chromodacryorrhea, a lean appearance, and/or ptosis. All animals showed weight loss or reduced body weight gain and reduced food consumption during the treatment period. Necropsy of the high dose animals found gelatinous contents in the gastrointestinal tract or parts thereof, and emaciation. The researchers determined the main cause for moribundity in the high dose group was forestomach ulceration and/or hyperplasia of the squamous epithelium of the forestomach. Other histopathological changes noted at this dose level included: lymphoid atrophy of the thymus, correlating to a reduced size of the thymus at necropsy; hyperplasia and inflammation of the forestomach; hyperplasia of the villi in the duodenum and jejunum; foamy macrophages and sinusoidal dilation and congestion/ erythrophagocytosis in the mesenterial lymph node; absence of spermiation and degeneration of spermatids in the testes, oligospermia and seminiferous cell debris in the epididymides, and reduced contents in the prostate and seminal vesicles, which corresponded to a reduced size of seminal vesicles, prostate and epididymides at necropsy. The results of this study were used to determine the doses for a reproduction/developmental toxicity test.[2]

Dermal – Non-Human

Stearamidopropyl Dimethylamine

A dermal 90- day repeated dose toxicity study of stearamidopropyl dimethylamine was performed in accordance to OECD Guideline 411 in groups of 5 male and 5 female New Zealand White rabbits.[2] Test solutions were prepared fresh weekly in distilled, 30%/70% ethanol/water for each group. The test material was applied at doses of 0%, 0.25%, or 10% w/v (equivalent to 0, 5, or 200 mg/kg/day, respectively) in a dose volume of 2 ml/kg/day to intact rabbit skin once daily, 5 days/week for 13 consecutive weeks. Test sites were not occluded.

Clinical signs of toxicity were observed daily and necropsy and histological examinations were performed at the end of the treatment period.

No mortality was observed during the study. Slight conjunctivitis was observed in 1 control animal and 2 animals in the 0.25% dose group, which was not related to the test material. Animals that received 0.25% test material had moderate or slight erythema, slight edema, slight desquamation and slight fissuring. Animals that received 10% test material were observed with moderate erythema, slight edema, slight desquamation and slight fissuring. No treatment-related changes in body weight and body weight gain were observed during the study. No test-related biologically significant changes were noted in the absolute and relative liver, kidney and adrenal weight determinations. Statistically significant increases in white blood cell values were noted in the 10% dose group. In addition, there was an increase in platelet values from baseline to necropsy of the 0.25% dose group. The changes in white blood cells of the 10% dose group were attributed to the chronic stress of collaring and not considered to be related to the test material. The significant increase in platelet values of the 0.25% dose group was a result of low baseline values. At necropsy, the treated skin in both the 0.25% and 10% dose groups had a dry hair coat with an accumulation of test material on the surface. Histopathological examinations revealed minimal acanthosis and hyperkeratosis at the treatment sites of all treated groups. The incidence and severity were similar in both groups. Incidental non-treatment related histopathological changes were noted in several other tissues such as brain, liver, kidney, prostate and pancreas. The researchers in this study determined the systemic no observed adverse effect level (NOAEL) of stearamidopropyl dimethylamine was greater than 10% w/v in 30%/70% ethanol/water (equivalent to 200 mg/kg bw/day).[2]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Stearamidopropyl Dimethylamine

The effects of stearamidopropyl dimethylamine (100% active ingredient) on reproduction and development were studied in 10 Wistar rats/sex/dose by oral gavage in accordance to OECD guideline 421.[2] Dose levels tested were 0, 20, 70 and 200 mg/kg body weight/day at a dose volume of 5 ml/kg body weight. Parental males were exposed to the test material 2 weeks prior to mating, during mating, and up to study termination. Parental females were exposed 2 weeks prior to mating, during mating, during gestation, and during at least 4 days of lactation. In the 200 mg/kg males, a weight loss of up to 15% of day 1 weight was observed during the first 2 weeks of treatment, but this effect seemed to recover during the treatment period. The mean body weight and body weight gain of the 200 mg/kg males remained statistically significantly lower throughout treatment. Females of the same dose group had statistically significant reduced body weight gain during the first 2 weeks of treatment, as well as during gestation. Food intake was reduced during the entire premating period for males, and during the first week of the premating period for the females. Additionally, the feed consumption of the females remained slightly lower throughout pregnancy and lactation. No other treatment-related changes were observed in the parental animals.

The non-statistically significant decrease in the mean number of corpora lutea was observed in the 70 and 200 mg/kg dose groups when compared with the control animal; however, a statistically significant lower number of implantation sites were noted in the 200 mg/kg dose group females. A statistically significant lower number of living pups was noted in the 70 and 200 mg/kg dose groups. No other treatment-related changes were noted in any of the remaining reproductive parameters investigated in this study (i.e. mating, fertility and conception indices and precoital time, testes and epididymides weights, spermatogenic staging profiles). Based on the results of this study on stearamidopropyl dimethylamine, the researchers determined the paternal NOAEL to be 70 mg/kg body weight/day, the maternal NOAEL to be 70 mg/kg body weight/day, and the developmental NOAEL to be 200 mg/kg body weight/day.[2]

In the dermal 90-day repeated dose toxicity study in rabbits described above, no treatment-related findings concerning the reproductive organs were observed. [2]

The dermal developmental toxicity potential of stearamidopropyl dimethylamine was studied in 80 artificially inseminated New Zealand White rabbits. [2] Groups of 20 rabbits received the test material at 0, 5, 100, or 200 mg/kg body weight/day at a dose volume of 2 ml/kg body weight during days 7 through 18 of gestation. The test material was applied to the clipped backs of the rabbits as a solution in 30% isopropanol and 70% reverse osmosis membrane processed deionized water. The test sites were not occluded and were rinsed with water 2 h after each application. The rabbits were observed daily during and after the dosage periods for clinical signs of toxicity, skin irritation, mortality, abortion, delivery, body weight, and feed consumption. All rabbits were killed on day 29 and complete gross necropsy was performed. The uteri were examined for pregnancy, number of implantations, live and dead fetuses and early and late resorptions. Corpora lutea were counted. Each fetus was weighed and subsequently examined for gross external variations and gender, prior to examination for soft tissue and skeletal variations.

No mortalities were observed during the course of the study. Clinical signs attributed to administration of the test material included alopecia (5, 100, 200 mg/kg/day doses), excess lacrimation (100 and 200 mg/kg/day dosages), ungroomed coat and green-colored matted fur around mouth and rump (200 mg/kg/day dosage). Statistically significant ($p \leq 0.05$ to $p \leq 0.01$) increases in the incidences of rabbits with these signs occurred only in the mid and high dose groups, when compared with the controls. Dose-dependent skin reactions including atonia, desquamation and fissuring were observed in mid and high dose groups. One high dose group rabbit had eschar present, attributed to the treatment. Two low dose group rabbits aborted on day 21 of gestation and 1 rabbit in the high dose group delivered prematurely; however, these events were not test material-related. Body weight gains were significantly decreased in the mid-dose ($P \leq 0.05$) and high dose ($P \leq 0.01$) group animals. High dose group animals had a significant decrease ($P \leq 0.01$) in average body weight during treatment, and continued to have lower average body weights than control rabbits during the post dosage period. Body weight and bodyweight gain of low dose group rabbits were comparable to control values. When compared to the control values, maternal feed consumption was affected in the mid- and high dose groups, with the average daily feed consumption of the high dose group rabbits significantly decreased ($P \leq 0.05$ to $P \leq 0.0.1$) from Day 15 through Day 21 of gestation.

Slightly impaired implantation and slightly decreased litter size was observed in the 200 mg/kg dose when compared to the control group, but this effect was not statistically significant ($p > 0.05$). All of the values were within expected historical control values. The test material did not adversely affect pregnancy incidence or average numbers of corpora lutea or resorptions. Viable fetuses were present in 20, 14, 17, and 14 litters from control, low, middle, and high dosage groups, respectively. One rabbit each from low and high dose group had all implantations resorbed. No treatment-related fetal variations at gross external, soft tissue or skeletal examination were observed. The researchers concluded that dermal application of stearamidopropyl dimethylamine in rabbits during gestation days 7 through 18 did not produce evidence for developmental toxicity. The maternal NOEL was determined to be 5 mg/kg body weight/day and the NOAEL was determined to be100 mg/kg body weight/day based on variations in body weight and food consumption data.[2]

GENOTOXICITY

Stearamidopropyl Dimethylamine

The mutagenic potential of 85% stearamidopropyl dimethylamine was studied in reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvr A, with and without S9 metabolic activation.[31] The test concentrations ranged from 5-5000 µg/plate. The positive controls were 2-nitrofluorene, 9-aminoacridine, sodium azide, methyl methane sulfonate, and 2-aminoanthracene. The test material was cytotoxic at $\geq$ 50 µg/plate in *S. typhimurium* and $\geq$500 µg/plate in *E. coli*. No biologically relevant increases in revertant colony numbers were observed in any test strain at any dose level, with or without metabolic activation. Controls yielded expected results. It was concluded that stearamidopropyl dimethylamine was not mutagenic in this assay.

The mutagenic potential of 100% pure stearamidopropyl dimethylamine in ethanol was studied for cell mutation in mouse lymphoma L5178Y TK+/- cells in accordance with OECD guideline 467 in 2 independent experiments.[2] Concentrations tested were 0.003 to 60 µg/ml, and the experiments were performed with and without 8% or 12% S9 metabolic activation. No statistically significant positive effects with or without S9 activation were observed in either experiment. Positive controls yielded the expected results. It was concluded that stearamidopropyl dimethylamine was not mutagenic in this assay.

The genotoxic potential of stearamidopropyl dimethylamine in ethanol was studied in a chromosome aberration study using human peripheral blood lymphocytes in accordance with OECD guideline 473.[2] In this 2 part study, the test material was tested up to 10 µg/ml, without and with S9 metabolic activation, in experiment 1; and in experiment 2, the test material was tested up to 25and 10 µg/ml, without and with S9, respectively. Incubation for cells in the first experiment was 3 h, without and with metabolic activation; and in the second experiment, incubation was 3 h and 24 h or 48 h, without and with metabolic activation, respectively. In both experiments, no statistically or biologically significant increased number of cells with chromosomal aberrations were observed both with and without metabolic activation. Solvent and positive controls yielded expected results. Under the conditions of this study, stearamidopropyl dimethylamine was not considered clastogenic.

CARCINOGENICITY

No studies were found on the carcinogenicity potential of fatty acid amidopropyl dimethylamines.

IRRITATION AND SENSITIZATION

The North American Contact Dermatitis Group (NACDG) evaluated 25,813 patients for allergic contact dermatitis with patch tests from 1998 to 2007.[32] "Amidoamine" produced relevant allergic reactions in 0.5% of the seniors (20/4215; ages ≥ 65), 0.7% of the adults (136/20,162; ages 19 to ≤ 64), and 0.7% of the children (10/1436; ages ≤ 18) tested.

Ocular irritation studies and dermal irritation and sensitization studies are summarized in Tables 4, 5, and 6, respectively. No to minimal irritation was observed in ocular irritation assays of behenamidopropyl dimethylamine and dilinoleamidopropyl dimethylamine. All but one ocular irritation study of stearamidopropyl dimethylamine report no to minimal irritation; the exception found severe ocular irritation when tested at 100% in rabbit eyes. Stearamidopropyl dimethylamine were considered not irritating in non-human studies when tested at 100%. Behenamidopropyl dimethylamine (up to 3%), 1% oleamidopropyl dimethylamine diluted by 10%, and 0.045% stearamidopropyl dimethylamine in personal care products were not irritating in several in-use studies. Behenamidopropyl dimethylamine at 0.3% diluted to 1%, 4% brassicamidopropyl dimethylamine, and stearamidopropyl dimethylamine at 2% neat or diluted to 30% in hair conditioners were not contact sensitizers. However, irritation reactions were observed.

CLINCIAL USE

Case Reports

Oleamidopropyl Dimethylamine

In the Netherlands, 13 female patients were reported to have allergic contact dermatitis to a baby lotion that contained 0.3% oleamidopropyl dimethylamine.[33,34] Reactions were especially prevalent when applied to damaged skin and/or the periorbital area. To investigate the possibility of cross-reactions, these patients were patch tested with oleamidopropyl dimethylamine (0.4%), ricinoleamidopropyl dimethylamine lactate (0.5%), stearamidopropyl dimethylamine lactate (0.5%), behenamidopropyl dimethylamine (0.5%), isostearamidopropyl dimethylamine (0.3%), tallowamidopropyl dimethylamine (0.3%), lauramidopropyl dimethylamine (0.2%), myristamidopropyl dimethylamine (0.05%), cocamidopropyl dimethylamine (0.1%), minkamidopropyl dimethylamine (0.1%), and palmitamidopropyl dimethylamine (0.025%). The test solutions were prepared by adding water to the raw material, unless the material was insoluble, then phosphoric acid was added until a clear solution formed. All 13 patients reacted to the oleamidpropyl dimethylamine. One patient had no reactions to any of the other substances, but 12 patients had reactions to at least 4 of the related substances: ricinoleamidopropyl dimethylamine lactate and tallowamidopropyl dimethylamine (11 patients, 85%), lauramidopropyl dimethylamine (9 patients out of 12 tested, 75%), and myristamidopropyl dimethylamine (6 patients, 46%). Five patients reacted to isostearamidopropyl dimethylamine, minkamidopropyl dimethylamine, and cocamidopropyl dimethylamine (only 12 patients tested). The remaining substances elicited response in only 1 or 2 patients. The author of this study could not rule out that some of these reactions may have been irritant reactions.

In another Dutch report, one medical practitioner reported on 3 cases of allergic contact dermatitis in patients that had used a body lotion.[35] In the first case, a 32-year-old female had itchy swelling of the eyelids. Both the upper and lower lids were edematous, red and scaly. The symptoms disappeared a few days following use of corticosteroid ointment and avoidance of cosmetics. Patch tests showed the patient was allergic to balsam of Peru and a body lotion that the patient had used around the eyes for several years. When tested with the lotion's ingredients, the patient had a positive reaction to oleamidopropyl dimethylamine.

In the second case, a 21-year-old was reported to have itchy dermatosis around the eyes and diffuse itching of the body. Upon examination, only mild desquamation was observed on the upper eyelids. The symptoms disappeared within a week of avoiding her cosmetics. Patch tests showed the patient was allergic to nickel cobalt and a body lotion that she had been using. The patient had positive reactions to oleamidopropyl dimethylamine and quaternium-15 when tested with the lotion's ingredients.

The third case, a 29-year-old female with a history of atopic dermatitis and no active dermatitis reported dry and itchy skin. Scratch tests were positive for several inhalant allergens. Patch tests showed a positive reaction to a body lotion she had been using. Doubtful reactions were observed to hydroxycitronellal and quaterium-15. Further tests showed a positive reaction to oleamidopropyl dimethylamine. The itching improved after the patient discontinued using the body lotion.[35]

Oleamidopropyl Dimethylamine and Cocamidopropyl Dimethylamine

A 10-year retrospective study of patients with allergic eyelid dermatitis investigated the possible allergens.[36] Patch testing was performed in these patients with the NACDG's standard screening tray and other

likely allergen trays. Out of 46 patients with confirmed allergic eyelid dermatitis, 5 (10.9%) had relevant reactions to oleamidopropyl dimethylamine and 2 (4.3%) had relevant reactions to cocamidopropyl dimethylamine.

RELEVANT DATA FROM PREVIOUS CIR SAFETY ASSESSMENTS

The sensitization studies and case reports of DMAPA and amidoamine that the Panel reviewed in the safety assessment of cocamidoporpyl betaine (CAPB) have been summarized in Table 7 and Table 8, respectively.[1] *In the tables, amidoamine refers to cocamidopropyl dimethylamine.*

SUMMARY

The fatty acid amidopropyl dimethylamines, referred to as "amidoamines" function primarily as antistatic agents in cosmetic products. The CIR Expert Panel has expressed great concern about these chemicals in a safety assessment of fatty acid amidopropyl betaines, in which fatty acid amidopropyl dimethylamines were noted as impurities with sensitizing potential.

Fatty acid amidopropyl dimethylamines have the core structure of a fatty acid amide, *N*-substituted with 3-propyl-*N'*,*N'*-dimethylamine. These ingredients are manufactured by the amidization (i.e., amide forming condensation) of fatty acids with 3,3-dimethylaminopropylamine (DMAPA), most commonly under alkaline or acidic conditions. Although nitrosamine content has not been reported, fatty acid amidopropyl dimethylamines are composed of secondary amides and tertiary amines, and potentially can be nitrosated. Therefore, fatty acid amidopropyl dimethylamine should be formulated to avoid the formation of nitrosamines.

Of the ingredients in this safety assessment, stearamidopropyl dimethylamine has the most reported uses in cosmetic and personal care products, with a total of 427; 355 of those uses are in rinse-off formulations. Behenamidopropyl dimethylamine has the second greatest number of overall uses reported, with a total of 35; 32 of those uses are in rinse-off formulations. For both ingredients, most of the rinse-off uses are in hair conditioners. A few uses were reported each for brassicamidopropyl dimethylamine, cocamidopropyl dimethylamine, isostearamidopropyl dimethylamine, lauramidopropyl dimethylamine, minkamidopropyl dimethylamine, oleamidopropyl dimethylamine, and palmitamidopropyl dimethylamine. No uses were reported to the VCRP for the remaining fatty acid amidopropyl dimethylamines.

In a survey of use concentrations conducted by the Personal Care Products Council, stearamidopropyl dimethylamine is reported to be used at a range of maximum concentrations of 0.01%-5%, with 5% reported in non-coloring hair conditioners. In behenamidopropyl dimethylamine, the range of maximum concentrations was reported to be 0.3%-3%, with 3% reported in non-coloring hair conditioners. A range of maximum concentrations for cocamidopropyl dimethylamine was reported to be 0.03%-6.5%, with 6.5% reported in skin cleansing products. No use concentrations were reported for almondamidopropyl dimethylamine; avocadoamidopropyl dimethylamine; babassuamidopropyl dimethylamine; minkamidopropyl dimethylamine; oatamidopropyl dimethylamine; oliveamidopropyl dimethylamine; sesamidopropyl dimethylamine; tallamidopropyl dimethylamine.

The amidoamine ingredients in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.

Myristamidopropyl dimethylamine has reported uses as a biocide in contact lens disinfecting solution.

In a QSAR model, the dermal absorption of stearamidopropyl dimethylamine has been estimated to be 0.04 mg and 0.12 mg after 8 and 24 h, respectively, with absorbed fractions being 0% at each time period. The maximum dermal absorption rate was calculated to be 2.40×10^{-6} mg/cm^2/h.

The LD_{50} values in two acute oral toxicity studies of stearamidopropyl dimethylamine in rats were > 2000 mg/kg body weight and 1396 mg/kg body weight, respectively.

Systemic toxicity was observed in an oral 14 day dose range finding rat study of stearamidopropyl dimethylamine at a dose of 500 mg/kg body weight/day. In rabbits, the systemic NOAEL of stearamidopropyl dimethylamine in a dermal repeated dose study was greater than 10% w/v in 30%/70% ethanol water (equivalent to 200 mg/kg bw/day).

In an oral reproduction and developmental toxicity study of stearamidopropyl dimethylamine tested up to 200 mg/kg body weight/day in rats, the researchers determined the paternal NOAEL to be 70 mg/kg body weight/day, the maternal NOAEL to be 70 mg/kg body weight/day, and the developmental NOAEL to be 200 mg/kg body weight/day. The dermal application of stearamidopropyl dimethylamine tested up to 200 mg/kg body weight/day in rabbits during gestation days 7 through 18 produced no evidence of developmental toxicity. The maternal NOEL was determined to be 5 mg/kg body weight/day and the NOAEL was determined to be100 mg/kg body weight/day based on variations in body weight and food consumption data in this study.

No studies were found on the carcinogenicity of fatty acid amidopropyl dimethylamines. Stearamidopropyl dimethylamine was not genotoxic in a reverse mutation assay, a cell mutation assay in mouse lymphoma, or a chromosome aberration study in human peripheral blood lymphocytes.

No to minimal irritation was observed in ocular irritation assays of behenamidopropyl dimethylamine and dilinoleamidopropyl dimethylamine. All but one ocular irritation study of stearamidopropyl dimethylamine report no to minimal irritation; the exception found severe ocular irritation when tested at 100% in rabbit eyes.

In a NACDG retrospective analysis, 'amidoamine" produced relevant allergic reactions in 0.5% -0.7% of seniors, adults, and children tested, respectively.

Behenamidopropyl dimethylamine at concentrations up to 3% and 0.045% stearamidopropyl dimethylamine in personal care products were not irritation in several in-use studies. Behenamidopropyl dimethylamine at 0.3% diluted to 1%, 4% brassicamidopropyl dimethylamine, and stearamidopropyl dimethylamine at 2% neat or diluted to 30% were not contact sensitizers. However, irritation reactions were observed.

Possible cross-reactions to several fatty acid amidopropyl dimethylamines were observed in patients that were reported to have allergic contact dermatitis to a baby lotion that contained 0.3% oleamidopropyl dimethylamine.

A 10-year retrospective study found that out of 46 patients with confirmed allergic eyelid dermatitis, 10.9% had relevant reactions to oleamidopropyl dimethylamine and 4.3% had relevant reactions to cocamidopropyl dimethylamine.

Several cases of allergic contact dermatitis were reported in patients from the Netherlands that had used a particular type of body lotion that contained oleamidopropyl dimethylamine.

Researchers have included the CAPB impurities, DMAPA and amidoamine, in the scope of sensitization and case studies and have found that one or both of the impurities may be the responsible agent for contact allergy to CAPB.

DRAFT DISCUSSION

In past ingredient safety assessments, the CIR Expert Panel had expressed concern over *N*-nitrosation reaction in ingredients containing amine groups. Fatty acid amidopropyl dimethylamines contain secondary amides and tertiary amines that may serve as substrates for *N*-nitrosation. Additionally, these ingredients may contain secondary amine impurities which may serve as substrates for *N*-nitrosation. Therefore, the Expert Panel recommended that these ingredients should not be included in cosmetic formulations containing *N*-nitrosating agents.

The Expert Panel also expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

The Panel discussed the issue of incidental inhalation exposure from cologne, indoor tanning products, and other propellant and pump spray products. No inhalation data were identified or provided. These ingredients reportedly are used at concentrations up to 2% in cosmetic products that may be aerosolized. The Panel noted that 95% – 99% of droplets/particles 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, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects. The Panel considered other data available to characterize the potential of fatty acid amidopropyl dimethylamines to cause systemic toxicity, irritation, sensitization, or other effects. They noted no safety concerns for these substances from the results of acute and repeated dose toxicity studies and genotoxicity studies. Additionally, little or no irritation was observed in multiple tests of dermal and ocular exposure. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

The CIR Expert Panel has expressed concern in the previous fatty acid amidopropyl betaines safety assessment about the impurities that may exist in the amidopropyl betaines because of their sensitizing potential. These impurities, the fatty acid amidopropyl dimethylamines, are the ingredients discussed in this safety assessment. The Panel especially recognizes that there are rising concerns over oleamidopropyl dimethylamine and the potential for contact sensitization from this ingredient, which has recently been added to the North American Contact Dermatitis Group's test panel. The Panel reviewed relevant animal and human data related to all of these ingredients and determined that additional are data needed. The additional data needed are:

- percutaneous absorption of the ingredient that has the shortest chain fatty acids (e.g., lauramidopropyl dimethylamine), and if it is absorbed;
- reproduction and developmental toxicity data; and

- sensitization and irritation data on oleamidopropyl dimethylamine at use concentration.

DRAFT CONCLUSION

The CIR Expert Panel concluded that the available data or information are insufficient to make a determination that the fatty acid amidopropyl dimethylamines listed below are safe under the intended conditions of use:

almondamidopropyl dimethylamine*
avocadamidopropyl dimethylamine*
babassuamidopropyl dimethylamine*
behenamidopropyl dimethylamine
brassicamidopropyl dimethylamine
cocamidopropyl dimethylamine
dilinoleamidopropyl dimethylamine*
isostearamidopropyl dimethylamine
lauramidopropyl dimethylamine
linoleamidopropyl dimethylamine*
minkamidopropyl dimethylamine
myristamidopropyl dimethylamine*
oatamidopropyl dimethylamine*
oleamidopropyl dimethylamine
olivamidopropyl dimethylamine*
palmitamidopropyl dimethylamine
ricinoleamidopropyl dimethylamine*
sesamidopropyl dimethylamine*
soyamidopropyl dimethylamine*
stearamidopropyl dimethylamine
sunflowerseedamidopropyl dimethylamine*
tallamidopropyl dimethylamine*
tallowamidopropyl dimethylamine*
wheat germamidopropyl dimethylamine*

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

TABLES AND FIGURES

Table 1. Names, CAS registry numbers, and definitions.[16] (wherein the italicized or bracketed text has been added by CIR staff)

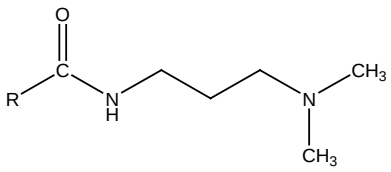
Ingredient & CAS No.	Definition
Almondamidopropyl Dimethylamine	Almondamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from almond oil. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from almond oil.
Avocadamidopropyl Dimethylamine	Avocadamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from Persea Gratissima (Avocado) Oil. This amidoamine *results from the reaction of DMAPA and* the fatty acids derived from Persea Gratissima (Avocado) Oil.
Babassuamidopropyl Dimethylamine	Babassuamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from Orbignya oleifera (babassu) oil. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from Orbignya oleifera (babassu) oil.
Behenamidopropyl Dimethylamine 60270-33-9 [872429-01-1]	Behenamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and behenic acid.*
Brassicamidopropyl Dimethylamine	Brassicamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from Brassica Campestris (Rapeseed) Seed Oil. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from Brassica Campestris (Rapeseed) Seed Oil.
Cocamidopropyl Dimethylamine 68140-01-2	Cocamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from coconut oil. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from coconut oil.
Dilinoleamidopropyl Dimethylamine [120174-68-7]	Dilinoleamidopropyl Dimethylamine is the condensation product of Dilinoleic Acid and aminopropyl dimethylamine. *Dilinoleamidopropyl Dimethylamine is the amidoamine that results from the reaction of DMAPA and the 36-carbon dicarboxylic acid, formed by the catalytic dimerization of linoleic acid.*
Isostearamidopropyl Dimethylamine 67799-04-6 [3432-14-2]	Isostearamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and isostearic acid.*
Lauramidopropyl Dimethylamine 3179-80-4 [1002119-56-3] [872428-97-2]	Lauramidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and lauric acid.*
Linoleamidopropyl Dimethylamine 81613-56-1	Linoleamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and linoleic acid.*
Minkamidopropyl Dimethylamine 68953-11-7	Minkamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from mink oil. *This amidoamine results from the reaction of DMAPA and* the fatty groups derived from mink oil.
Myristamidopropyl Dimethylamine 45267-19-4 [872428-98-3]	Myristamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and myristic acid.*
Oatamidopropyl Dimethylamine	Oatamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from Avena Sativa (Oat) Kernel Oil. *This amidoamine results from the reaction of DMAPA and the fatty acids derived from Avena Sativa (Oat)* Kernel Oil.
Oleamidopropyl Dimethylamine 109-28-4 [149879-92-5] [126150-52-5]	Oleamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and oleic acid.*
Olivamidopropyl Dimethylamine	Olivamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from olive oil. *This amidoamine* results *from the reaction of DMAPA and* the fatty acids derived from olive oil.

Table 1. Names, CAS registry numbers, and definitions.[16] (wherein the italicized or bracketed text has been added by CIR staff)

Ingredient & CAS No.	Definition
Palmitamidopropyl Dimethylamine 39669-97-1 [872428-99-4]	Palmitamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and palmitic acid.*
Ricinoleamidopropyl Dimethylamine 20457-75-4	Ricinoleamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and ricinoleic acid.*
Sesamidopropyl Dimethylamine	Sesamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from sesame oil. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from sesame oil.
Soyamidopropyl Dimethylamine 68188-30-7	Soyamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from soy. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from soy.
Stearamidopropyl Dimethylamine 7651-02-7 20182-63-2 [78392-15-1]	Stearamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). *This amidoamine results from the reaction of DMAPA and stearic acid.*
Sunflowerseedamidopropyl Dimethylamine	Sunflowerseedamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from sunflower seed oil. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from sunflower seed oil.
Tallamidopropyl Dimethylamine 68650-79-3	Tallamidopropyl Dimethylamine is the substituted amine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from tall oil. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from tall oil.
Tallowamidopropyl Dimethylamine 68425-50-3	Tallowamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from tallow. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from tallow.
Wheat Germamidopropyl Dimethylamine	Wheat Germamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from wheat germ oil. *This amidoamine results from the reaction of DMAPA and* the fatty acids derived from wheat germ oil.

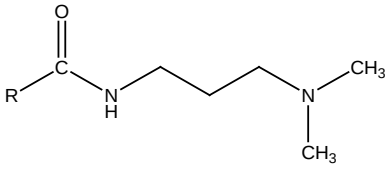
Figure 2. Structures

1. Almondamidopropyl Dimethylamine



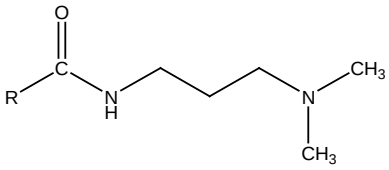
wherein RC(O) represents any of the fatty acid residues derived from almond oil

2. Avocadamidopropyl Dimethylamine



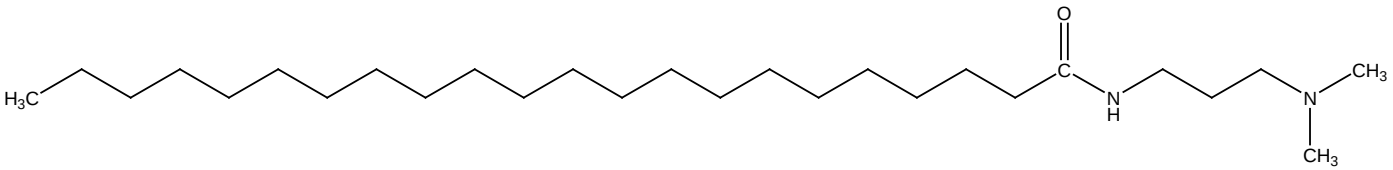
wherein RC(O) represents any of the fatty acid residues derived from Persea Gratissima (Avocado) Oil

3. Babassuamidopropyl Dimethylamine

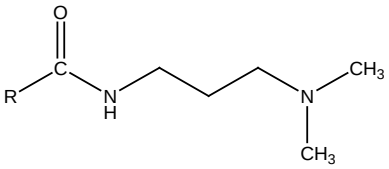


wherein RC(O) represents any of the fatty acid residues derived from Orbignya oleifera (babassu) oil

4. Behenamidopropyl Dimethylamine

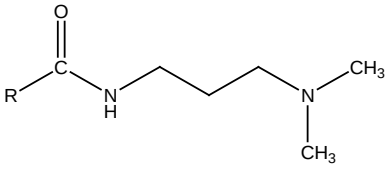


5. Brassicamidopropyl Dimethylamine



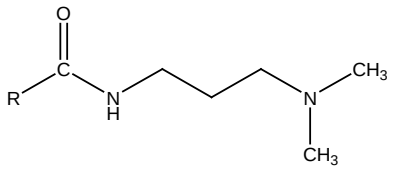
wherein RC(O) represents any of the fatty acid residues from Brassica Campestris (Rapeseed) Seed Oil

6. Cocamidopropyl Dimethylamine



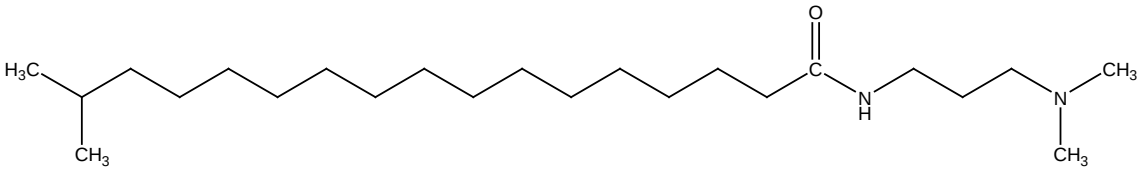
wherein RC(O) represents any of the fatty acid residues derived from coconut oil

7. Dilinoleamidopropyl Dimethylamine

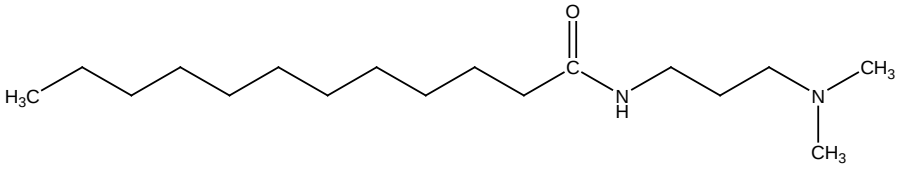


wherein RC(O) represents the variety of 36-carbon dicarboxylic acid residues, formed by the catalytic dimerization of linoleic acid

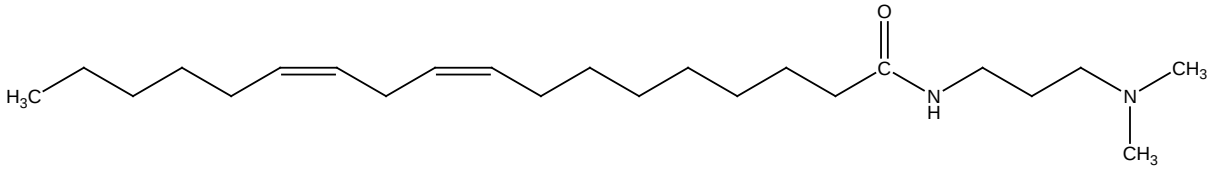
8. Isostearamidopropyl Dimethylamine (one example of an "iso")



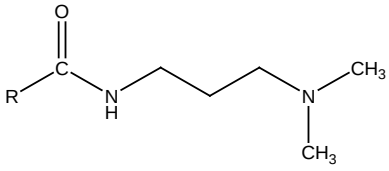
9. Lauramidopropyl Dimethylamine



10. Linoleamidopropyl Dimethylamine

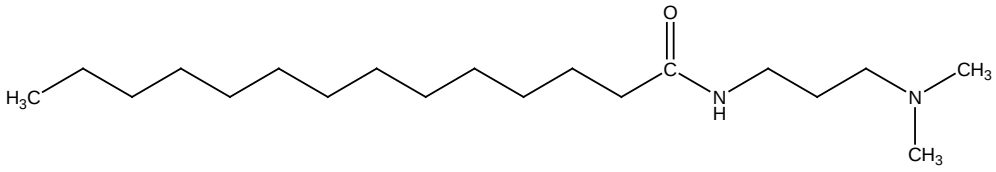


11. Minkamidopropyl Dimethylamine

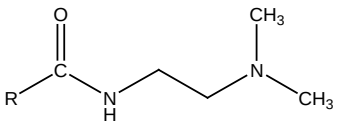


wherein RC(O) represents any of the fatty acid residues derived from mink oil

12. Myristamidopropyl Dimethylamine

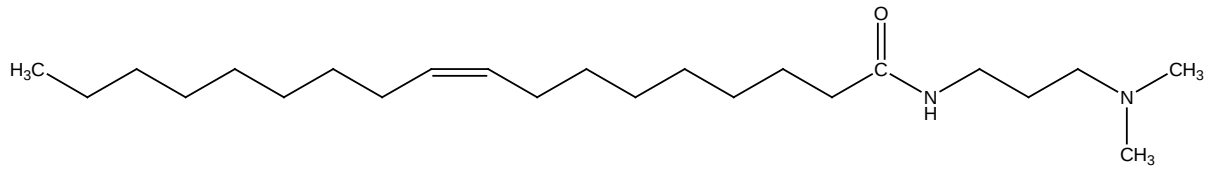


13. Oatamidopropyl Dimethylamine

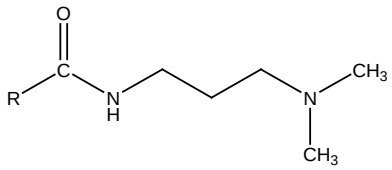


wherein RC(O) represents any of the fatty acid residues derived from Avena Sativa (Oat) Kernel Oil

14. Oleamidopropyl Dimethylamine

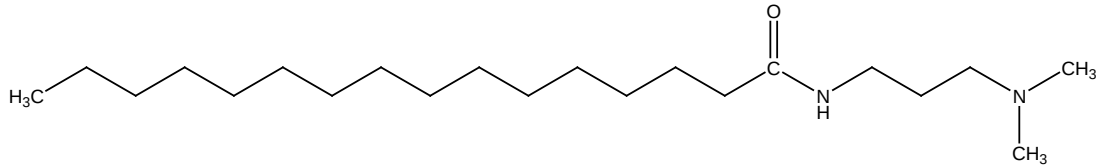


15. Olivamidopropyl Dimethylamine

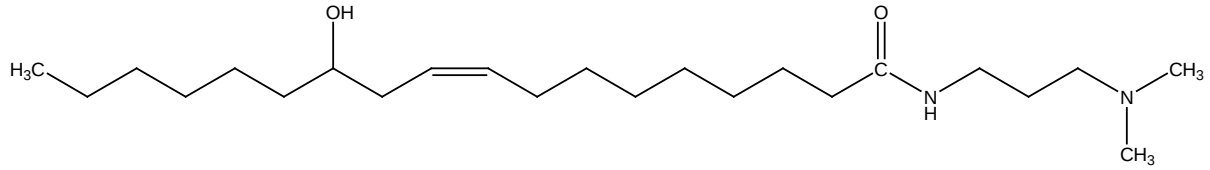


wherein RC(O) represents any of the fatty acid residues derived from olive oil

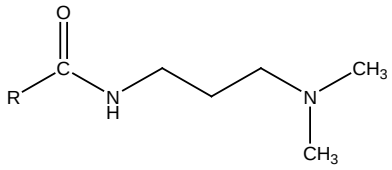
16. Palmitamidopropyl Dimethylamine



17. Ricinoleamidopropyl Dimethylamine

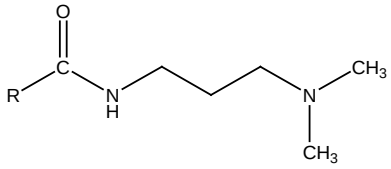


18. Sesamidopropyl Dimethylamine



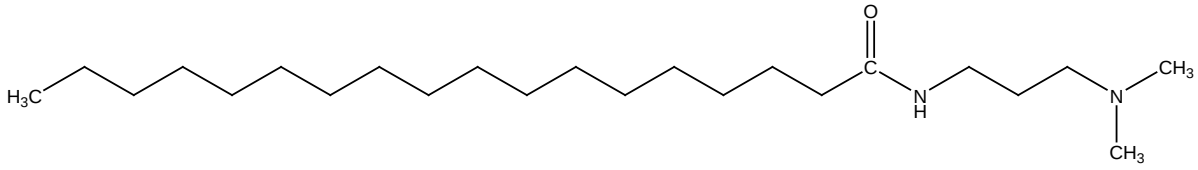
wherein RC(O) represents any of the fatty acid residues derived from sesame oil

19. Soyamidopropyl Dimethylamine

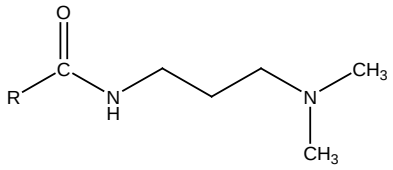


wherein RC(O) represents any of the fatty acid residues derived from soy

20. Stearamidopropyl Dimethylamine

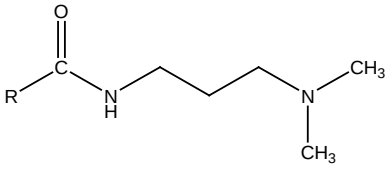


21. Sunflowerseedamidopropyl Dimethylamine



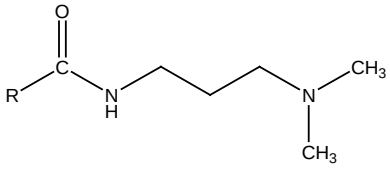
wherein RC(O) represents any of the fatty acid residues derived from sunflower seed oil

22. Tallamidopropyl Dimethylamine



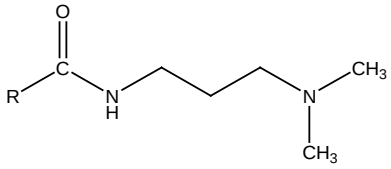
wherein RC(O) represents any of the fatty acid residues derived from tall oil

23. Tallowamidopropyl Dimethylamine



wherein RC(O) represents any of the fatty acid residues derived from tallow

24. Wheat Germamidopropyl Dimethylamine



wherein RC(O) represents any of the fatty acid residues derived from wheat germ oil

Table 2. Physical and chemical properties.

Property	Value	Reference
Behenamidopropyl Dimethylamine		
Molecular Weight g/mol	424.75	[37]
Molecular Volume cm^3/mol @ 20 °C	487.4	[37]
Density/Specific Gravity g/cm^3 @ 20 °C	0.871	[37]
Vapor pressure mmHg@ 25 °C	6.30×10^{-12}	[37]
Boiling Point °C	544.8	[37]
log P @ 25 °C	9.656	[37]
Cocamidopropyl Dimethylamine		
Appearance	Clear liquid	[8]
Odor	Mild amine	[8]
Density/Specific Gravity g/cm^3 @ 25 °C	0.98-1.02	[8]
Vapor pressure mmHg	< 0.01	[8]
Boiling Point °C @ 760 mmHg	> 100	[8]
Melting Point °C	< 25	[8]
Solubility in water	Soluble	[8]
pH	~ 9	[8]
Lauramidopropyl Dimethylamine		
Molecular Weight g/mol	284.48	[37]
Molecular Volume cm^3/mol @ 20 °C	322.3	[37]
Density/Specific Gravity g/cm^3 @ 20 °C	0.882	[37]
Vapor pressure mmHg@ 25 °C	3.17×10^{-7}	[37]
Boiling Point °C	418.9	[37]
Melting Point °C	28.5-30.0	[5]
log P @ 25 °C	4.561	[37]

Table 2. Physical and chemical properties.

Property	Value	Reference
Linoleamidopropyl Dimethylamine		
Molecular Weight g/mol	364.61	[37]
Molecular Volume cm^3/mol @ 20 °C	408.6	[37]
Density/Specific Gravity g/cm^3 @ 20 °C	0.892	[37]
Vapor pressure mmHg@ 25 °C	2.69×10^{-10}	[37]
Boiling Point °C	504.3	[37]
log P @ 25 °C	6.805	[37]
Myristamidopropyl Dimethylamine		
Molecular Weight g/mol	312.53	[37]
Molecular Volume cm^3/mol @ 20 °C	355.3	[37]
Density/Specific Gravity g/cm^3 @ 20 °C	0.879	[37]
Vapor pressure mmHg@ 25 °C	3.84×10^{-8}	[37]
Boiling Point °C	445.8	[37]
log P @ 25 °C	5.580	[37]
Oleamidopropyl Dimethylamine		
Physical Form	Liquid	[11]
Color	Amber	[11]
Molecular Weight g/mol	366.62	[37]
Molecular Volume cm^3/mol @ 20 °C	414.9	[37]
Density/Specific Gravity g/cm^3 @ 20 °C	0.883	[37]
Vapor pressure mmHg@ 25 °C	2.57×10^{-10}	[37]
Boiling Point °C	504.8	[37]
Solubility	Slightly in water, readily when neutralized with acid	[11]
log P @ 25 °C	7.209	[37]
pH @ 25 °C	9.0-10.0	[11]

Table 2. Physical and chemical properties.

Property	Value	Reference
Palmitamidopropyl Dimethylamine		
Molecular Weight g/mol	340.59	[37]
Molecular Volume cm^3/mol @ 20 °C	388.3	[37]
Density/Specific Gravity g/cm^3 @ 20 °C	0.876	[37]
Vapor pressure mmHg@ 25 °C	4.52×10^{-9}	[37]
Boiling Point °C	471.8	[37]
log P @ 25 °C	6.599	[37]
Ricinoleamidopropyl Dimethylamine		
Molecular Weight g/mol	382.62	[37]
Molecular Volume cm^3/mol @ 20 °C	412.8	[37]
Density/Specific Gravity g/cm^3 @ 20 °C	0.926	[37]
Vapor pressure mmHg@ 25 °C	8.20×10^{-14}	[37]
Boiling Point °C	537.9	[37]
log P @ 25 °C	5.395	[37]
Stearamidopropyl Dimethylamine		
Physical Form	Waxy flake	[13]
Molecular Weight g/mol	368.64	[37]
Molecular Volume cm^3/mol @ 20 °C	421.7	[37]
Density/Specific Gravity g/cm^3 @ 20 °C	0.874	[37]
Vapor pressure mmHg@ 25 °C	5.19×10^{-10} - 9.03×10^{-10}	[37]
Boiling Point °C	490.6 - 496.9	[37]
Melting Point °C	58.5-59.5; 65-70	[5,13]
log P @ 25 °C	7.618 - 7.629	[37]

Table 3a. Frequency and concentration of use according to duration and type of exposure.[17,18]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Behenamidopropyl Dimethylamine		**Brassicamidopropyl Dimethylamine**		**Cocamidopropyl Dimethylamine**	
Totals*	**43**	**0.3-3**	**1**	**0.2-4**	**9**	0.003-6.5
Duration of Use						
Leave-On	3	1	NR	0.2	5 (3)	0.03
Rinse-Off	40 (32)	0.3-3	1	4	4 (3)	0.003-6.5
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	NR	NR	NR	0.2	9 (6)	0.03-6.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	43 (35)	0.3-3	1	4	NR	0.003
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	2 (1)	1.3-5
Baby Products	NR	NR	NR	NR	NR	NR

	Isostearamidopropyl Dimethylamine		**Lauramidopropyl Dimethylamine**		**Minkamidopropyl Dimethylamine**	
Totals*	**13**	**0.04-0.38**	**2**	**NR**	**1**	**NR**
Duration of Use						
Leave-On	1	0.04	NR	NR	NR	NR
Rinse Off	12	0.38	2 (1)	NR	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	1	0.04	1 (NR)	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	12	0.38	1	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1 (NR)	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Oleamidopropyl Dimethylamine		**Palmitamidopropyl Dimethylamine**		**Stearamidopropyl Dimethylamine**	
Totals*	**12**	**0.0015-1**	**1**	**NR**	**472**	**0.01-5**
Duration of Use						
Leave-On	5	0.0015-1	1	NR	75 (72)	0.02-3
Rinse-Off	7	0.8	NR	NR	397 (355)	0.01-5
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	1.5-1.8
Incidental Ingestion	NR	NR	NR	NR	NR	1.7
Incidental Inhalation-Spray	NR	0.15 pump spray	NR	NR	NR	1.8-2
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	1.7
Dermal Contact	NR	1	NR	NR	25 (28)	0.01-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	12	0.0015-0.8	1	NR	353 (315)	0.05-5
Hair-Coloring	NR	NR	NR	NR	94 (83)	0.3-2
Nail	NR	NR	NR	NR	NR (1)	NR
Mucous Membrane	NR	NR	NR	NR	NR	1.7-1.8
Baby Products	NR	NR	NR	NR	1	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.

NR – no reported uses

3b. Ingredients not reported in use.

almondamidopropyl dimethylamine
avocadamidopropyl dimethylamine
babassuamidopropyl dimethylamine
dilinoleamidopropyl dimethylamine
linoleamidopropyl dimethylamine
myristamidopropyl dimethylamine
oatamidopropyl dimethylamine
olivamidopropyl dimethylamine
ricinoleamidopropyl dimethylamine
sesamidopropyl dimethylamine
soyamidopropyl dimethylamine
sunflowerseedamidopropyl dimethylamine
tallamidopropyl dimethylamine
tallowamidopropyl dimethylamine
wheat germamidopropyl dimethylamine

Table 4. Non-human ocular irritation studies.

Ingredient	Concentration	Method	Results	Reference
In Vitro				
Behenamidopropyl Dimethylamine	0.3% in a shampoo, diluted with deionized water to a 10% solution	EpiOcular irritation study	No/minimal irritation	[38,39]
Behenamidopropyl Dimethylamine	0.3% in a shampoo, diluted with deionized water to a 10% solution	EpiOcular irritation study	No/minimal irritation	[39,40]
Stearamidopropyl Dimethylamine	0.045% in a pre-shave scrub, diluted to 10% solution	EpiOcular irritation study	No/minimal irritation	[41]
Stearamidopropyl Dimethylamine	2% in a hair conditioner, diluted to 10% solution	EpiOcular irritation study	No/minimal irritation	[42]
Stearamidopropyl Dimethylamine	100% in pellet form	Bovine corneal opacity and permeability (BCOP) test method performed according to OECD Guideline 437; test material was washed at least 3 times after 4 h incubation with test substance; GLP compliant	Mean in vitro irritancy score was 29 (threshold for corrosive/severe irritant is $\geq$ 55.1); not severely irritating/not corrosive	[2]
In Vivo				
Dilinoleamidopropyl Dimethylamine	In a 2% dilution with corn oil	Eye irritation study in a single male rabbit (strain not described)	No irritation	[43]
Stearamidopropyl Dimethylamine	100% in pellet form	Eye irritation study in a single male New Zealand White rabbit performed according to OECD Guideline 405; ~0.1 ml test material instilled into conjunctival sac of one eye; eye was not rinsed after application; GLP compliant	Severe irreversible effects on the eye consisting of injury to the cornea (opacity max. grade 2), iridial irritation (grade 1), ad severe effect on the conjunctivae; fluorescein examination not performed due to bloody discharge	[2]

Table 5. Dermal irritation studies

Ingredient	Concentration	Method	Results	Reference
Non-Human				
Stearamidopropyl Dimethylamine	100% in pellets	In vitro skin irritation study (EPISKIN model) according to OECD Guideline 439; exposure to test tissue 15 min; GLP compliant	Not irritating	[2]
Stearamidopropyl Dimethylamine	100% active material tested as 0.5 g in 0.7 ml water	In vivo skin irritation study in 3 New Zealand White rabbits according to OECD Guideline 404; semi-occluded patches (6 cm^2) on clipped skin; 1 animal exposed for 3 min, 1 h, and 4 h; remaining 2 animals exposed for 4 h; GLP compliant	No skin reactions following the 3 min and 1 h applications; very slight edema observed 1 h after patch removal in all 3 animals; very slight erythema observed 1 h after patch removal in 2 animals; very slight to slight erythema and very slight to slight edema were noted in all 3 animals 24, 48 h, and 72 h after patch removal; reactions were fully reversible in 1 animal within 7 days and in the remaining 2 within 15 days; study classified this material as not irritating to rabbit skin	[2]
Human				
Behenamidopropyl Dimethylamine	3% in a hair conditioner	Two week daily use study in 28 female subjects	No dermal irritation or other adverse events	[44]
Behenamidopropyl Dimethylamine	0.3% in a shampoo	Two week daily use study in 28 female subjects	No dermal irritation or other adverse events	[45]
Oleamidopropyl Dimethylamine	1% oil, diluted by 10% in an aqueous solution	48 h patch test in 102 subjects; semi-occluded 2 cm^2 webril patch	No dermal irritation or other adverse events	[46]
Stearamidopropyl Dimethylamine	0.045% in a pre-shave scrub	Two week daily use study in 30 male subjects	No dermal irritation	[47]

Table 6. Dermal sensitization studies

Ingredient	Concentration	Method	Results	Reference
Non-Human				
Stearamidopropyl Dimethylamine	2.5% for intradermal induction, 1% for dermal induction, 2% in challenge; vehicle was paraffin oil	Guinea pig maximization using 10 Dunkin Hartley female guinea pigs for the test material	Non-sensitizing; however, mild and moderate skin reactions and necrosis were observed after both sets of inductions	[48]
Stearamidopropyl Dimethylamine	NA	QSAR modeling for sensitization using TOPKAT	Not sensitizing – no compounds sufficiently similar to the query structure were found	[49]
Human				
Behenamidopropyl Dimethylamine	0.3% in a shampoo, prepared as a 1% v/v aq. solution	HRIPT; occlusive with 0.2 ml sample; 106 subjects completed	No dermal sensitization or other adverse events	[50]
Behenamidopropyl Dimethylamine	0.3% in a shampoo, prepared as a 1% v/v aq. solution	HRIPT; occlusive with 0.2 ml sample; 103 subjects completed	No dermal sensitization or other adverse events	[51]
Brassicamidopropyl Dimethylamine	4% in a hair masque, tested neat	HRIPT; semi-occlusive with 0.2 ml sample; 102 subjects completed	No skin reactivity observed	[52]
Stearamidopropyl Dimethylamine	2% in a hair conditioner, diluted to a 1% aq. soln.	HRIPT; occlusive; 104 subjects completed	No significant potential for eliciting dermal irritation or sensitization	[53]
Stearamidopropyl Dimethylamine	0.045% in a body lotion	HRIPT; occlusive with 0.2ml sample; 102 subjects completed	No adverse events	[54]
Stearamidopropyl Dimethylamine	0.045% in a pre-shave scrub, 1% dilution in deionized water	HRIPT; occlusive with 0.2 ml sample on a 2 cm^2 patch; 104 subjects completed	43/104 subjects had barely perceptible (+) to mild (1) irritant responses, which were not considered clinically meaningful. No induced contact allergy	[55]
Stearamidopropyl Dimethylamine	0.75% in a rinse-off hair conditioner, 2% dilution in deionized water	HRIPT; occlusive with a 0.2 ml sample on a 2 cm^2 patch; 106 subjects completed	1 subject had (++) erythema and edema on 6^{th} induction patch, which was determined to be possible contact dermatitis. Overall, study concluded no sensitization	[56]
Stearamidopropyl Dimethylamine	0.5% in a leave-on hair conditioner	HRIPT; semi-occlusive with a 0.02ml sample on a 1cm^2 patch; 55 subjects completed	No irritation or sensitization	[57]
Stearamidopropyl Dimethylamine	0.5% in a leave-on hair conditioner	HRIPT; semi-occlusive with a 0.02 ml sample on a 1 cm diameter patch; 56 subjects completed	No irritation or sensitization	[58]
Stearamidopropyl Dimethylamine	0.05% in a face and neck product	HRIPT; occlusive with a 25-38 mg/cm^2 sample on a patch; 50 subjects completed	No irritation or sensitization	[59]
Stearamidopropyl Dimethylamine	2% in a hair conditioner, tested neat	HRIPT; semi-occlusive with a 0.2 g sample on a 4 cm^2 patch; 104 subjects completed; estimated dose/unit area = 1000 μg/cm^2	Not a dermal sensitizer	[54]
Stearamidopropyl Dimethylamine	2% in a hair conditioner, diluted to 30% (w/v) with distilled water	HRIPT; occlusive with a 0.3 ml sample on a 4 cm^2; 100 subjects completed; estimated dose/unit area = 300 μg/cm^2	Not a dermal sensitizer	[60]
Stearamidopropyl Dimethylamine	2% in a hair conditioner, diluted to 30% (w/v) with distilled water	HRIPT; occlusive with a 0.15 ml sample on a 4 cm^2 patch; 122 subjects completed; estimated dose/unit area = 300 μg/cm^2	Mild erythema observed in several subjects on 1or more days in induction phase. In challenge phase, 10 subjects exhibited mild erythema. Test material determined to be an irritant; no evidence of delayed contact hypersensitivity	[61]
Stearamidopropyl Dimethylamine	2% in a hair conditioner, diluted to 30% (w/v) with distilled water	HRIPT; occlusive with a 0.2 ml sample on a 4 cm^2 patch; 107 subjects completed; estimated dose/unit area = 300 μg/cm^2	In induction phase, 2 subjects exhibited mild erythema; a 3rd had mild erythema with edema and papules. In challenge phase, 3 subjects observed with mild erythema. Test material was a primary irritant, no evidence of delayed contact hypersensitivity	[62]

Estimated dose/unit area = concentration x amount x density x unit conversion x area

Table 7. Sensitization studies of DMAPA and amidoamine previously reviewed by the CIR Expert Panel.[1]

Substances	Concentrations	Method	Results	Reference
Sensitization Studies – Non-Human				
Stearamidopropyl dimethylamine	Induction with 1.0% w/v test material in 80% ethanol/20% distilled water; challenge with 0.25% w/v test material in acetone; rechallenge with 0.25%, 0.125%, and 0.0625% w/v	Delayed contact hypersensitivity study in 20 Hartley outbred guinea pigs with 25-mm diameter occluded Hill Top chambers on clipped, intact skin; induction applied for 6 h/wk for total of 3 exposures at a dose volume of 0.3 ml [estimated dose/unit area = 6.1 x 102 µg/cm^2]; exposure sites were rinsed after removal of chambers; control group of 10 guinea pigs received the vehicle alone; primary challenge patches on naïve skin after 2 week rest [estimated dose/unit area = 1.5 x 102 µg/cm^2].	One guinea pig had delayed contact hypersensitivity to the test material; control animals had no reactions. A rechallenge was conducted in 6 guinea pigs 13 days after the primary challenge; an additional 5 animals were used as controls. One guinea pig had a positive response to the test material at 0.25%. No other reactions were observed.	63
Palmityl/stearylamidopropyl dimethylamine	25% active material in 8.95% phosphoric acid and 66.05% water; rechallenge with 0.25% and 0.5% active material	Delayed contact hypersensitivity in 10 male and 10 female albino Dunkin/Hartley guinea pigs with 4 cm^2 occluded patches on clipped skin; induction applied 6h/wk for a total of 3 3xposures at a dose volume of 0.4 ml [estimated dose/unit area = 2.5 x 10^4 µg/cm^2]; control group was 10 untreated animals; primary challenge patches on naïve skin after 2 week rest	All but 3 of the 20 guinea pigs had patchy to severe erythema at the 24 and 48 h observation periods; 4 control animals had slight to moderate patchy erythema during the observation periods. A rechallenge was conducted; no sensitization was observed with the 0.25% active material, but 0.5% active material elicited reactions in sensitized animals.	64
cocamidopropyl dimethylamine	0.1% test material in DOBS/saline vehicle and Freund's complete adjuvant (50/50 ratio) for intradermal injections; 5% test material in acetone/PEG400 for the induction patch; 0.5% test material in acetone/PEG 400 for challenge patch	Maximization study in 10 albino Dunkin/Hartley guinea pigs (6 females and 4 males); a single occlusive 48-h induction patch (2 x 4 cm) of 0.2-0.3 ml a week following intradermal injections; control group was 4 male animals received intradermal injections and induction patches using only the vehicle mixture; single occlusive 24-h challenge patch (8-mm diameter in a Finn chamber) after a 2 week rest; 2 more challenges were made 1 and 2 weeks after the first challenge; reactions were scored on a scale of 0 (no reaction) to 3 (severe erythema and edema)	At the first challenge, 7 animals had a reaction score $\geq$ 0.5 at 24 h after the removal of the patch. After 48 h, 6 animals had a reaction score $\geq$ 0.5. Three out of 10 animals had a reaction score of 2. At the second challenge, 7 guinea pigs had a score $\geq$ 0.5 24 h after patch removal. These scores were consistent at the 48-h reading. Five of 10 animals had a reaction score of 2. At the third challenge, all 10 guinea pigs had a score $\geq$ 1 24 h after patch removal. These score remained largely consistent at the 48-h reading. Eight of the 10 animals had a reaction score of 2.	65
cocamidopropyl dimethylamine	0.025% test material for intradermal injections; 1% test material for topical induction; 0.5% test material in acetone/PEG 400 for challenge patch	Guinea pig maximization study conducted in the same manner as above except 4 female guinea pigs were used as controls and only 2 challenges were made	At the first challenge, 3 animals had a reaction score $\geq$ 1 at both the 24 and 48 h readings, with one of the animals scoring a 2. At the second challenge, 3 animals had a reaction score $\geq$ 1 at 24 and 48 h readings, although 1 animal had no reaction at 48 that had one at 24 h while another that had no reaction at 24 h had one at 48 h.	65

Table 7. Sensitization studies of DMAPA and amidoamine previously reviewed by the CIR Expert Panel.[1]

Substances	Concentrations	Method	Results	Reference
DMAPA (99.0+% pure), plus 3 other recognized human contact allergens	0.5%, 1.0%, 2.5%, 5.0%, or 10.0% of the test material in 8 different vehicles: acetone, olive oil [4:1], dimethylsulfoxide, methylethylketone, dimethyl formamide, propylene glycol, and 50:50 and 90:10 mixtures of ethanol and water	LLNA study in groups of 4 female CBA/Ca mice	At 10.0% DMAPA, the stimulation indices (SI) ranged from 2.2 in propylene glycol to 15.7 in dimethyl formamide. The estimated concentrations for a SI of 3 (EC_3) ranged from 1.7% (in dimethyl formamide) to >10% (in propylene glycol).	66
Stearamidopropyl Dimethylamine (TEGO AMID S 18) with a DMAPA concentration ≤ 20 ppm, amine concentration 150.8 mg KOH/g (limit range = 148.0-152.0 mg KOH/g), and melting point 68.0°C (limit range 66.0-69.0°C).	0.1%, 0.5%, 1%, 2.5%, or 5% (w/v) of the test material in ethanol/water (7/3, v/v); control was vehicle only; positive control was α-hexylcinnamaldehyde in acetone:olive oil (4:1, v/v)	LLNA study in groups of 4 CBA/Ca female mice	No deaths occurred during the treatment period in any dose group and no clinical signs of toxicity were observed during treatment in the control group or in the 0.1% and 0.5% dose groups. Slight to moderate ear erythema was observed after the second or third application at both dosing sites in all mice in the 1%, 2.5%, and the 5% dose groups that persisted for 2 days in the 1% dose group and until treatment end in the 2.5% and 5% dose groups. Body weight was not affected in any of the animals. The SI were 1.4, 2.1, 2.1, 5.8, and 3.9 for the 0.1%, 0.5%, 1%, 2.5%, and 5% dose groups, respectively. The EC_3 was calculated as 1.4%. The positive control group had the expected results.	67,68
Cocamidopropyl Dimethylamine (~99% C12-C18)	0%, 0.1%, 0.5%, 1%, 2.5%, or 5% of the test material in ethanol/water, 7:3 (v/v) neutralized to pH 6.0 with citric acid monohydrate; positive control was 35% hexylcinnamaldehyde.	LLNA in groups of 5 mice	Very slight erythema was observed on day 3 and very slight erythema and edema were observed on days 4-6 of the 2.5% dose group; in the 5% dose group, 4 of the 5 mice treated had very slight erythema and very slight edema on day 2. On days 3-6, mice in this dose group had well defined erythema and slight edema. The SI were 1.8, 1.0, 3.1, 24.5, and 60.6 for the 0.1%, 0.5%, 1%, 2.5%, or 5% dose groups, respectively. The EC_3 was calculated as 0.98%. The positive control group had the expected results.	69
Predictive Sensitization Studies - Human				
Stearamidopropyl Dimethylamine	0.25% w/v in undiluted mineral oil	HRIPT with 112 subjects; 0.3 ml sample on Webril patches	Frequent incidences of slight to moderate irritation, including erythema, some edema, papules, glazing, and cracking observed during induction period, but considered transient. Five subjects had a reaction of Grade 1 or greater during challenge phase. Responses to test material were considered indicative of primary irritation rather than contact sensitization.	70
Stearyl/palmitylamidopropyl Dimethylamine	4% aqueous liquid fabric softener formulation containing 0.5% of the test material	HRIPT with 77 subjects; 0.5 ml sample on a ¾ inch square Webril pad [estimated dose/unit area = 6.9×10^2 µg/cm^2]	The test material caused some irritation in most volunteers during induction. Eight subjects reacted at challenge, and 7 of the eight submitted to rechallenge with 4% and 0.4% aqueous formulations. No reactions indicative of sensitization occurred at rechallenge.	71

Table 7. Sensitization studies of DMAPA and amidoamine previously reviewed by the CIR Expert Panel.[1]

Substances	Concentrations	Method	Results	Reference
Oleamidopropyl Dimethylamine along with CAPB (1% aq.) and DMAPA (1% aq.)	0.5% aq.	HRIPT with a supplemented European standard series in 285 consecutive dermatitis patients	Twenty-three patients (8%) had allergic responses to DMAPA, 14 patients (4.9%) had allergic responses to DMAPA and oleamidopropyl dimethylamine, and 8 patients (2.8%) had allergic responses to all three of the supplemental chemicals. Analyses by TLC of the oleamidopropyl dimethyl amine sample revealed contamination with DMAPA (6 ppm or 0.12% of the sample) and indicated that the allergic responses to the 3 test substances in the last group were not attributable to cross-reactivity. (From study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	72
CAPB and DMAPA as well as positive patients' personal cosmetics diluted in water at 1:10, 1:100, and 1:1000	up to 1% for CAPB in water; up to 1% for DMAPA in petrolatum	2-year study of 1190 eczema patients using standard technique and grading according to the European Contact Dermatitis Group (ECDG)	17 patients were diagnosed with allergic contact dermatitis to CAPB. Relevance established with an additional positive patch test score of 2+ or more to at least one personal care product containing CAPB used by the patients. 15 patients were further tested with 12 patients tested with their personal cosmetics, of which 9 had positive reactions to at least one dilution and 5 had irritant reactions. All except 3 patients, who were not tested, had 2 or 3+ reaction to DMAPA at concentrations as low as 0.05%. One patient had a positive reaction to CAPB. The presence of DMAPA was investigated via thin-layer chromatography in the personal cosmetics of 4 of the patients that had positive reactions. The positive reactions to DMAPA suggest that the positive reaction to CAPB-containing products was likely attributable to DMAPA present as an impurity. DMAPA was measured in the products at 50 - 150 ppm. The concentration of DMAPA was also measured in the 2 CAPB types: one had a concentration of DMAPA at 200 ppm and DMAPA was below the detection limit (detection limit value not reported) in the other type. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	73
CAPB (30% active ingredient), amidoamine, DMAPA, monochloroacetic acid, and Tego 103 G	up to 1% aq. CAPB, DMAPA, and Tego 103 G, respectively, and up to 0.05% amidoamine	1200 consecutive patients with dermatitis of various types were patch tested with European standard series supplemented with CAPB; patients that subsequently had allergic or irritant reactions to CAPB were then patch tested with the chemicals that were intermediates or reactants in the synthesis of CAPB (amidoamine, DMAPA, and monochloroacetic acid) along with a sample of CAPB of greater purity and Tego 103 G 1% aq.	Positive allergic reactions to CAPB observed in 46 subjects (3.8%) while irritant reactions were recorded in 15 subjects (1.25%). Of the 46 subjects, 30 had positive reactions to DMAPA 1% aq. In these 30 subjects, 3 and 16 were positive to purer grade of CAPB 0.5% aq. and CAPB 1% aq., respectively. Patients with irritant reactions had negative reactions to synthesis materials and purer grade of CAPB. No allergic or irritant reactions to DMAPA were observed in 50 healthy controls. No positive reactions to amidoamine 0.05% were observed. (From the study documentation, it was not possible to determine whether the administered CAPB concentrations were 0.5% active and 1% active or 0.5% aqueous and 1% aqueous, which would equate to 0.15% active and 0.3% active, respectively).	74

Table 7. Sensitization studies of DMAPA and amidoamine previously reviewed by the CIR Expert Panel.[1]

Substances	Concentrations	Method	Results	Reference
CAPB and sodium chloride and N, N-dimethyl-propylene-diaminotriacetic acid blend	1% aq, respectively	30 patients with a history of contact allergy to 1% aq. CAPB and 1% DMAPA were patch tested with pure CAPB and an impurity that was isolated from a sample of CAPB (Tego Betaine F 30% solution) by thin-layer chromatography and infrared spectrum analysis	None of the subjects reacted to any of the chemicals. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	[75]
DMAPA in various vehicles including water, SLES 2% aq. solution, and polysorbate-20 2% aq. solution, as well as to CAPB and 10 substances chemically related to DMAPA	0.00005% to 0.1% for DMAPA	34 subjects with confirmed contact allergy to 1% aq. DMAPA were patch tested to the various DMAPA solutions, CAPB, and the DMAPA-related substances; and a series of 10 substance; test sites were occluded for 2 days and the sites were scored for reactions on days 2, 3, 4, and 7.	18 subjects had positive reactions to DMAPA in water at 0.1%, no positive reactions were noted for DMAPA in water at 0.01% to 0.00005%. Positive reactions were observed with DMAPA in SLES, with 27 subjects positive at the highest concentration, 10 subjects positive at 0.01%, 5 subjects positive at 0.005%, and 1 subject positive at 0.0001%. Positive reactions were also observed with DMAPA in polysorbate-20 in 21 subjects at 0.1% and 4 subjects at 0.01%. Patch tests for the chemically related structures were positive in 28 subjects for N,N-dimethyl-2-ethylenediamine 1% aq., 12 subjects for cocamidopropylamine oxide 1% aq. (35% active material), and 18 subjects for CAPB 1% aq. (30% active material). No other reactions occurred.	[76]
DMAPA in surfactant solutions (1% or 2% w/w surfactants) that included purified CAPB (DMAPA < 1 ppm), SLES, polysorbate20 (Tween20), lauryl polyglucoside (APG), SLES/CAPB 3:1 (w/w), and APG/CAPB 3:2 (w/w)	Serial dilutions of DMAPA up to 100 ppm	20 patients with confirmed non-occupational contact allergy to DMAPA (1% aq.) and CAPB (1% aq.) and an intolerance to detergents and shampoos	Positive reactions observed with DMAPA at 1 ppm and higher in 1% CAPB (1 reaction each to 1 ppm and 5 ppm DMAPA, 3 reactions to 10 ppm DMAPA, and 4 reactions to 50 ppm DMAPA). Similar positive observations were made with DMAPA in 1% SLES/CAPB 3:1. No positive reactions were observed when DMAPA (100 ppm) was tested in water, but 7 positive reactions were recorded when the material was tested in 2% CAPB. A greater number of reactions were observed when 100 ppm DMAPA was mixed with 2% SLES/CAPB (5 reactions) than when mixed with 2% APG/CAPB (2 reactions). The authors noted that CAPB and SLES/CAPB 3:1 act as carriers for DMAPA when applied under occlusion at 1%, and that surface activity in more concentrated surfactant solutions may be responsible for allergic reactions to DMAPA. (From the study documentation, it was not possible to determine whether the administered CAPB concentrations were 1% active and 2% active or 1% aqueous and 2% aqueous, which would equate to 0.3% active and 0.6%, respectively).	[77]
DMAPA and CAPB	1% pet. and 1% aq. for DMAPA and 1% aq. CAPB with a maximum residual DMAPA <15 ppm.	80 subjects (mainly hairdressers) with dermatitis from 1996 to 1999 patch tested with the hairdresser's series supplemented with DMAPA	Of the 80 subjects, 6 had + to +++ reactions to CAPB; none of these 6 had reactions to DMAPA. A housewife with scalp and neck dermatitis had a + reaction to DMAPA 1% aq. and a +? reaction to DMAPA 1% pet. This subject had no positive reaction to CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	[78]

Table 7. Sensitization studies of DMAPA and amidoamine previously reviewed by the CIR Expert Panel.[1]

Substances	Concentrations	Method	Results	Reference
Partially purified CAPB, cocamidopropylamine, DMAPA, and 1.0% pure CAPB	1% aq. CAPB containing <0.5% cocamidopropylamine, 0.1% and 0.01% cocamidopropylamine, 0 to 10,000 ppm DMAPA, 0.2% aq. DMAPA in SLS, 1.0% CAPB containing <0.3% cocamidopropylamine and <10 ppm DMAPA	4/7 subjects that had relevant dermatitis to CAPB following use of liquid soaps, and in one case, an eye make-up remover, patch tested with partially purified CAPB; 6/7 subjects patched tested with DMAPA, DMAPA in SLS, and 1.0% CAPB, on normal and tape stripped skin	One subject tested with the partially purified CAPB had a positive reaction that appeared only to cocamidopropylamine while another had a reaction only to CAPB; however irritancy could not be ruled out because the subject's patch sites were read only on one day. The other 2 patients had positive reactions to cocamidopropylamine and CAPB. Control subjects had negative patch results. 1 of the 6 subjects tested with DMAPA reacted to DMAPA on normal and tape-stripped skin at concentrations >1000 ppm. 3 of the 6 subjects reacted to DMAPA in 0.2% SLS (one at 10,000 ppm, one at 1000 to 10,000 ppm, and one at 100 to 10,000 ppm). None of the subjects reacted to the 1.0% pure CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	79
DMAPA, amidoamine, and CAPB	1% aq. CAPB (from 2 different suppliers), 1% aq. DMAPA, 0.1%-0.5% purified amidoamine	10 subjects with known CAPB allergy patch tested with CAPB, DMAPA, and amidoamine	All the subjects had ++ reactions to DMAPA at 1% and purified amidoamine at 0.5%. Most subjects also had ++ reactions to purified amidoamine at 0.25% and the remaining had + reactions to this concentration. 4 patients had positive reactions (++) to the purified amidoamine at 0.1%. No reactions were observed with 1 of the supplied CAPB, which was suggested to have a higher purity by the authors. Control patches in 20 volunteers were negative for amidoamine. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	80
CAPB and amidoamine	1.0% aq. CAPB, 1.0% amidoamine	Retrospective study of 957 patients in 2001 that had positive patch test results to 1.0% aq. CAPB and/or 1.0% amidoamine	49 patients had positive reactions to CAPB, amidoamine, or both. A follow-up evaluation in 35 patients was performed to establish the relevance of reactions to CAPB and amidoamine to the use of products containing these chemicals. 15 patients (42.9%) reacted to CAPB, 12 patients (34.3%) reacted to amidoamine, and 8 patients (22.8%) reacted to both. Of the 35 patients, 29 (83%) could identify products containing CAPB at home. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	81
CAPB and amidoamine	1.0% CAPB, 0.1% amidoamine	Retrospective study of 975 patients in 2001 with CAPB and/or amidoamine contact allergy	15 patients had positive patch test reactions to CAPB only, 25 had positive patch test reactions to amidoamine only, and 18 had positive reactions to both (58 patients total). Definite and probable relevance (known exposure to CAPB) was determined in 16 patients that tested positive for amidoamine and in 16 that tested positive for CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	82

Table 7. Sensitization studies of DMAPA and amidoamine previously reviewed by the CIR Expert Panel.[1]

Substances	Concentrations	Method	Results	Reference
CAPB and amidoamine	1% aq. CAPB. 0.1% aq. amidoamine	4913 patients patch tested for allergic contact dermatitis with an extended screening series of 65 allergens that included CAPB and amidoamine from January 1, 2001 to December 31, 2002	Positive results for CAPB observed in 2.8% of the patients while 2.3% were positive for amidoamine. Relevance of the CAPB and amidoamine reactions (present and past) was 90.9% and 85%, respectively. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	83
CAPB and DMAPA	1% aq. purified CAPB, 1% aq. DMAPA	429 Chinese patients with suspected contact allergy were patch tested with the European standard series supplemented with CAPB and DMAPA	9 patients had irritant reactions, 12 had questionable reactions, and 42 had + reactions to CAPB. No reactions to CAPB greater than ++ were observed. Also of the 429 patients, 76 were diagnosed with cosmetic allergic contact dermatitis. 27 of the 76 diagnosed with cosmetic allergic contact dermatitis and 15 (out of 353) of the non-cosmetic allergic contact dermatitis subjects had positive reactions to CAPB ($P<0.05$). Only 25 of the former and none of the latter had relevant reactions. 10 of the 429 patients had positive reactions to DMAPA, 8 of which were considered relevant. Six of the 10 patients also had positive reactions to CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	84
Provocative Sensitization Studies - Human				
CAPB, DMAPA, amidoamine, and other potential allergens	CAPB-F grade (active level of CAPB in shampoo was 5.0%; active level in hand soap and body wash was 5.2%), CAPB grades F and S (both 1% aq.), DMAPA (0.1% pet), amidoamine (0.1% aq.), sodium monochloroacetate (0.1% aq.)	Provocative use study of products containing CAPB in 10 subjects that had positive reactions to CAPB in routine patch testing. 10 control subjects were also enrolled. Study divided into 3 phases with 3 different test products: Phase I was a forearm wash test with the shampoo diluted to 10% in tap water. If no allergic reaction occurred in Phase I, subjects then entered Phase II of the study: i.e., daily use of shampoo as hair cleanser. Subjects proceeded to Phase III of the study if no allergic reactions to the shampoo occurred. In Phase III, the subjects used the shampoo, body wash, and hand soap for 3 weeks. At least 2 months after the product use tests, the subjects were patch tested with CAPB DMAPA, amidoamine, sodium monochloroacetate, a proprietary mixture of preservatives for CAPB, and other potential allergens (perfumes and preservatives) that were in the test product formulations. Control subjects were patched with 1% CAPB.	-Three subjects completed the product use phases without experiencing an allergic reaction. 7 subjects had erythema, scaling, and pruritus on the arms, face, and/or neck in either Phase I or II of the study. 1 subject that experienced a positive reaction in the first phase was asked to repeat the forearm use test with the CAPB-containing shampoo on the left arm and with a CAPB-absent shampoo on the right arm. The subject experienced a positive reaction on both arms, which was likely caused by the preservatives in the shampoo products (as shown through patch testing). In Phase III, 3 subjects had scalp, face, and/or neck and body dermatitis. -Patch testing was performed in 9 of the 10 subjects, with 6 subjects reacting to amidoamine. 5 of these 6 subjects had positive reactions during the product use phases. 2 subjects had reactions to the CAPB-F grade with preservative, 3 had reactions to CAPB-F grade without preservative, 1 reacted to the CAPB-S grade, and 1 reacted to the proprietary preservative mixture. 2 subjects had questionable reactions to DMAPA. No other adverse reactions were noted in the subjects. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	85

Table 7. Sensitization studies of DMAPA and amidoamine previously reviewed by the CIR Expert Panel.[1]

Substances	Concentrations	Method	Results	Reference
purified CAPB containing only 1 ppm amidoamine, CAPB grade F containing approximately 3000 ppm amidoamine, and amidoamine	concentrations of CAPB not reported, 0.01% and 0.1% amidoamine	Follow-up patch test with 7 of the subjects from the above provocative test	2 subjects had questionable reactions to the purified CAPB while there were 3 positive reactions to the CAPB-F grade, 4 positive reactions to the higher concentration of amidoamine, and 2 positive reactions to the lower concentration of amidoamine.	[85,86]
CAPB and DMAPA	CAPB (25% dilution; DMAPA below 1 ppm); 0.1%, 0.3%, and 1.0% dilutions of CAPB (CKKB); and 0.1%, 0.3%, and 1.0% dilutions of DMAPA	Provocative use test in 10 subjects that had positive reactions to CAPB. 20 volunteers served as controls for the study. Study divided into 3 phases with 3 different test products: Phase I, a 0.1 ml test sample of shower gel containing was applied, lathered for 1 minute, and rinsed on the subjects' forearms twice daily for 7 days; Phase II of the study consisted of patch testing to differentiate irritant reactions from allergic reactions and to reconfirm sensitivity to CAPB and DMAPA. The subjects were patch tested with CAPB (CKKB) and DMAPA; subjects that had no allergic reactions in Phase I participated in Phase III. In Phase III, the subjects used the shower gel or 4 weeks as they would normally.	No skin irritation was observed in Phase I of the study. 1 subject with a history of atopic dermatitis was removed from the study due to a flare. Another subject had an immediate "wheal like reaction" on days 3 and 6 that cleared within minutes. This subject continued the forearm test an extra week and had no further effect. In Phase II, one control had an irritating reaction to 1% CAPB. In the study group, 5 of the 10 subjects had a positive reaction to 1% CAPB and another 3 had marginal allergic and/or irritant reactions. 1 subject had a positive reaction to DMAPA but had no clear reaction to CAPB. Another subject that had a positive reaction to CAPB had a doubtful reaction to 1% DMAPA. 8 subjects did not react to DMAPA. Only 7 subjects participated in Phase III of the study (the other 2 were not available), and no adverse reactions were observed in these subjects. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	[87]

Table 8. Case reports of DMAPA and amidoamine previously reviewed by the CIR Expert Panel.[1]

Mode of Contact	Patient(s)	Indication	Reference
occupational exposures in chemical factory workers to DMPAPA and CAPB	50-year-old man who worked in a chemical factory which produced amines and a 54-year-old man who worked with DMAPA and CAPB	-First patient a developed a red itchy face that cleared after treatment with topical corticosteroids and a week away from work. The patient had 4 more episodes over 6 months with swelling and spreading to the neck, shoulders, arms and hands. Patching testing with the European series yielded a + reaction only to ethylenediamine. Further patch testing with other amines, including DMAPA, produced a positive reaction (++) to DMAPA. Patch testing with serial dilutions of DMAPA revealed a ++ reaction at 1%, a ?+ reaction at 0.1%, and negative reactions at 0.01% and 0.001%. 20 controls had negative reactions when patch tested with 0.1% and 1% DMAPA. DMAPA was being utilized at the factory where the patient worked to make CAPB. The dermatitis signs improved but did not completely clear when the patient was moved to another part of the plant to work. -In the second patient, an itchy red scaly face and right palm was observed that cleared over 2 weeks. The patient had 6 more episodes over the next year. The dermatitis was resolved after the patient avoided contact with DMAPA. Patch testing with the chemicals used at the chemical factory yielded a ++ reaction only to DMAPA (1% pet.) on day 3 of site scoring.	88
occupational exposures to shampoos and hand cleansers that may have contained DMAPA	34-year-old woman employed as an assistant nurse without earlier skin symptoms	Patient reported dermatitis that would clear during periods of leave from work, but would reappear as soon as the patient resumed work. The patient was patch tested with the standard series, an antimicrobial series, and a cosmetics series. This testing only yielded a positive reaction to nickel. Initially, the hand dermatitis was considered to be occupational irritant contact dermatitis. The patient was forced to leave her career because of the condition and experienced occasional relapses afterward. 4 years later, the patient was patched tested with the European standard series (minus nickel sulfate), an antimicrobial series, and a cosmetics series which included CAPB, oleamidopropyl dimethylamine, DMAPA, and coconut diethanolamide. Only DMAPA (>99% purity, 1% pet.) elicited a positive reaction with + readings on days 2 and 3 and a ++ reading on day 4.	89
baby shampoo containing CAPB	37-year-old woman with no history of atopic or seborrheic dermatitis	Patient reported to have a 5-month history of eyelid dermatitis. A family physician had instructed the patient to apply baby shampoo to the eyelids daily to treat an infection of the eyelids. Patch testing revealed a + reaction to CAPB and a ++ reaction to amidoamine (concentrations tested not reported). The dermatitis cleared after discontinuing use of the product.	90
dermatitis of face and eyelids from unknown substance, possibly facial cream, that worsened with patient's hair touched her face	39-year-old woman with personal history of eczema and asthma	Patient reported with a 6-month history of persistent dermatitis of the face and eyelids. The patient complained of a burning sensation, pruritus, erythema, and occasional swelling of the eyelids. Patch testing using the NACDG standard series; the preservatives, vehicles and cosmetics series; and the patient's facial creams was conducted. Concentrations of the materials tested were not reported. On day 4, the patient reacted positively to nickel sulfate (++), gold sodium thiosulfate (++), cobalt chloride (+), tosylamide formaldehyde resin (+), CAPB (+), amidoamine (+), DMAPA (+), and oleamidopropyl dimethylamine (+). The patient did not have a positive reaction to cocamide diethanolamide.	91
allergic contact dermatitis from unknown substance, possibly personal care products containing DMAPA	58-year-old housewife, a 36-year-old male office worker, and a 24-year-old hairdresser	Patients with allergic contact dermatitis underwent patch testing with several test types including the standard series, the cosmetics series, the hairdresser's series, and with their own personal care products. All 3 patients tested positive to DMAPA (reactions ranged from + to ++ on day 7), but were negative for CAPB. After the initial patch testing, the patients were further tested with serial dilutions of 1% aq. DMAPA and 1% aq. CAPB (concentrations tested were 0.1%, 0.2%, 0.5%, and 1% for each). The first patient had a +/- reaction to 1% CAPB only. The other patients had no reactions to CAPB at any concentration. Allergic responses were noted in all 3 patients to DMAPA at concentrations of 0.2% and higher (+/- to + at 0.2%, +/- to ++ at 0.5%, and + to +++ to 1%). (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active).	92
eyelid dermatitis to an unknown substance	42-year-old female	Patient reported with a 4 month history of severe recalcitrant eyelid dermatitis. The patient's condition did not improve after use of all eye makeup was discontinued. The patient presented with bilateral periorbital and postauricular erythema, and a biopsy found spongiotic dermatitis. Patch testing using a modified NACDG standard series and a comprehensive cosmetic series was conducted. On day 4, the patient had + reaction to 1% aqueous DMAPA, a + reaction to neomycin, and a +++ reaction to bacitracin. There were no reactions to CAPB or amidoamine.	93

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2012 FDA VCRP RAW DATA

05A - Hair Conditioner	60270339	BEHENAMIDOPROPYL DIMETHYLAMINE	39
05F - Shampoos (non-coloring)	60270339	BEHENAMIDOPROPYL DIMETHYLAMINE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	60270339	BEHENAMIDOPROPYL DIMETHYLAMINE	1
05I - Other Hair Preparations	60270339	BEHENAMIDOPROPYL DIMETHYLAMINE	2
05A - Hair Conditioner	999003493	BRASSICAMIDOPROPYL DIMETHYLAMINE	1
10A - Bath Soaps and Detergents	68140012	COCAMIDOPROPYL DIMETHYLAMINE	2
12A - Cleansing	68140012	COCAMIDOPROPYL DIMETHYLAMINE	2
12C - Face and Neck (exc shave)	68140012	COCAMIDOPROPYL DIMETHYLAMINE	2
12D - Body and Hand (exc shave)	68140012	COCAMIDOPROPYL DIMETHYLAMINE	1
12F - Moisturizing	68140012	COCAMIDOPROPYL DIMETHYLAMINE	1
12G - Night	68140012	COCAMIDOPROPYL DIMETHYLAMINE	1
05A - Hair Conditioner	67799046	ISOSTEARAMIDOPROPYL DIMETHYLAMINE	12
12D - Body and Hand (exc shave)	67799046	ISOSTEARAMIDOPROPYL DIMETHYLAMINE	1
05D - Permanent Waves	3179804	LAURAMIDOPROPYL DIMETHYLAMINE	1
10A - Bath Soaps and Detergents	3179804	LAURAMIDOPROPYL DIMETHYLAMINE	1
05A - Hair Conditioner	68953117	MINKAMIDOPROPYL DIMETHYLAMINE	1
05A - Hair Conditioner	109284	OLEAMIDOPROPYL DIMETHYLAMINE	6
05F - Shampoos (non-coloring)	109284	OLEAMIDOPROPYL DIMETHYLAMINE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	109284	OLEAMIDOPROPYL DIMETHYLAMINE	4
05I - Other Hair Preparations	109284	OLEAMIDOPROPYL DIMETHYLAMINE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	39669971	PALMITAMIDOPROPYL DIMETHYLAMINE	1
01C - Other Baby Products	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	1
05A - Hair Conditioner	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	286
05C - Hair Straighteners	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	2
05E - Rinses (non-coloring)	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	1
05F - Shampoos (non-coloring)	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	10
05G - Tonics, Dressings, and Other Hair Grooming Aids	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	35
05I - Other Hair Preparations	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	19
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	72
06B - Hair Tints	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	1
06C - Hair Rinses (coloring)	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	7
06H - Other Hair Coloring Preparation	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	14
11E - Shaving Cream	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	3

12A - Cleansing	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	1
12D - Body and Hand (exc shave)	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	2
12F - Moisturizing	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	16
12G - Night	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	1
12J - Other Skin Care Preps	7651027	STEARAMIDOPROPYL DIMETHYLAMINE	1

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Final Report of the Cosmetic Ingredient Review Expert Panel on the Safety Assessment of Cocamidopropyl betaine (CAPB)

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Abstract

Cocamidopropyl betaine (CAPB) and related amidopropyl betaines are zwitterions used mainly as surfactants in cosmetics. These cosmetic ingredients are similar in their chemistry, in particular with respect to the presence of 3,3-dimethylamino-propylamine (DMAPA) and fatty acid amidopropyl dimethylamine (amidoamine) impurities, which are known as sensitizers. The CIR Expert Panel concluded that because these ingredients present no other significant toxicity, when formulated to be nonsensitizing (which may be based on a quantitative risk assessment), these ingredients are safe for use as cosmetic ingredients in the practices of use and concentration of this safety assessment.

Keywords

cocamidopropyl betaine, CAPB, cosmetics, safety

Introduction

Cocamidopropyl betaine (CAPB) is a zwitterion used primarily as a surfactant in cosmetic products. A safety assessment for CAPB was published by the Cosmetic Ingredient Review (CIR) in 1991.[1] At that time, the CIR Expert Panel (the Panel) concluded that CAPB is safe for use in rinse off cosmetic products at the current levels of use, and the concentration of use for cosmetic products designed to remain on the skin for prolonged periods of time (leave-on products) should not exceed 3.0%. Because raw material CAPB is commonly supplied to product finishing houses as a 30% preformulation solution, a 3% solution would correspond to a 10% solution of a full-strength CAPB raw material solution. Frequently, these preformulation solutions are described as having an "activity" of the ingredient (eg, typical raw material CAPB has an activity of 30%). Accordingly, to prepare a 3% solution of a CAPB, from a CAPB preformulation solution with 30% activity, the preformulation solution would need to be diluted by a factor of 10.

Based on new published data that described sensitization in patients from use of rinse off products, new uses in aerosol products, and a substantial increase in the number of uses, the Panel reopened the final report on CAPB in 2007. The following report is a compilation of new data and summary data from the original safety assessment on CAPB and related amidopropyl betaines. Because of chemical similarities to CAPB, the available data may be extrapolated to all of the following related aminopropyl betaines, in a process termed read across:

- almondamidopropyl betaine,
- apricotamidopropyl betaine,
- avocadamidopropyl betaine,
- babassuamidopropyl betaine,
- behenamidopropyl betaine,
- canolamidopropyl betaine,
- capryl/capramidopropyl betaine,
- coco/oleamidopropyl betaine,
- coco/sunfloweramidopropyl betaine,
- cupuassuamidopropyl betaine,
- isostearamidopropyl betaine,
- lauramidopropyl betaine,
- meadowfoamamidopropyl betaine,
- milkamidopropyl betaine,

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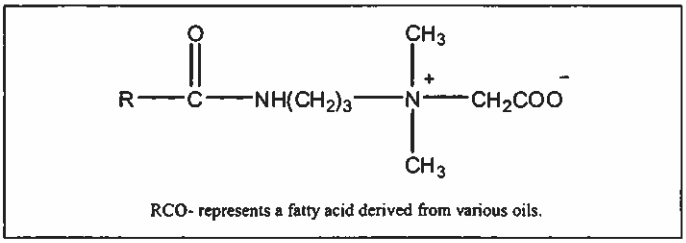

Figure 1. Amidopropyl betaine.

- minkamidopropyl betaine,
- myristamidopropyl betaine,
- oatamidopropyl betaine,
- oleamidopropyl betaine,
- olivamidopropyl betaine,
- palmamidopropyl betaine,
- palmitamidopropyl betaine,
- palm kernelamidopropyl betaine,
- ricinoleamidopropyl betaine,
- sesamidopropyl betaine,
- shea butteramidopropyl betaine,
- soyamidopropyl betaine,
- stearamidopropyl betaine,
- tallowamidopropyl betaine,
- undecyleneamidopropyl betaine, and
- wheat germamidopropyl betaine.

Chemistry

Definition and Structure

The general structure of amidopropyl betaines is as shown in Figure 1, where RCO- represents the fatty acids derived from various oils.[2] For example, for CAPB (CAS No. 61789-40-0), RCO- represents the fatty acids derived from coconut oil. Table 1 presents the definitions and structures of CAPB and related amidopropyl betaine ingredients.

Technical names for CAPB and its related amidopropyl betaines, as well as the functions these ingredients perform in cosmetics, are found in Table 2. There are numerous trade names and trade name mixtures containing CAPB and its related amidopropyl betaines.[2]

Physical and Chemical Properties

The CAPB is a clear, pale yellow liquid of medium viscosity (300-600 cps), with a slight fatty odor.[3,4] The CAPB has a boiling point of 230°F, a specific gravity of 1.04 relative to water, and no flash point.[5] The CAPB is soluble in water, ethanol, and isopropanol and insoluble in mineral oil.[3]

The CAPB is supplied as a solution in water and with sodium chloride (see Table 3). The concentration of CAPB in such supplied material is described by its activity.[6] The concentration of cosmetic-grade CAPB (active concentration) is what is left in the supplied solution after water (62%-66%) and sodium chloride (4.6%-5.6%) have been accounted for, which is ~30% of the supplied solution. In this report, unless a concentration has been reported as being active, a concentration of CAPB in solution will be calculated since it is unclear in some cases which is the true concentration that was tested. If, for example, a study reports the use of CAPB at 10% active, the assumption will be made that 10% active was tested. If a study reports use of 10% CAPB, concentrations will be calculated assuming both possibilities: (1) that it was 10% active or (2) it was 10% and only 30% of that was active, yielding 3% active.

Commercial grades containing concentrations of CAPB greater than 30% may contain solvents, such as propylene glycol. Although most commercial grades contain sodium chloride, low-salt products also are available. The concentration of sodium chloride in cosmetic grade CAPB ranges from 4.0% to 6.0%. Cosmetic grade CAPB may also contain a maximum of 3.0% glycerol.[1]

The fatty acid compositions of the oils that are components of the additional amidopropyl betaines described in this report are presented in Table 4.

Method of Manufacture

Figure 2 depicts the formation of CAPB through the reaction of coconut oil fatty acids (coconut oil or hydrolyzed, glyceryl-free coconut acid) with 3,3-dimethylaminopropylamine (DMAPA), which yields cocamidopropyl dimethylamine (amidoamine or dimethylaminopropyl cococamide). The amidoamine, a tertiary amine, is then reacted with sodium monochloroacetate to produce CAPB. In Figure 2, R represents the coconut fatty acid chain that varies between C-8 and C-18.[1,3,7-10]

Supplier information provided to the Personal Care Products Council (the Council) indicated that babassuamidopropyl betaine, coco/sunfloweramidopropyl betaine, cupuassuamidopropyl betaine, isostearamidopropyl betaine, lauramidopropyl betaine, meadowfoamamidopropyl (MF) betaine, oleamidopropyl betaine, ricinoleamidopropyl betaine, and wheat germamidopropyl betaine are manufactured in the same manner as CAPB.[11] Manufacturing data on the remaining amidopropyl betaines were not provided.

In cupuassuamidopropyl betaine, the intermediate is cupuassuamidopropyl dimethylamine, which can be found at a maximum level of 0.2% in the final product.[11] The DMAPA level in final cupuassuamidopropyl betaine product is 0.05%. In MF betaine, the intermediate is MF dimethylamine (MF-DMAPA), which can be found at less than 0.5% in the final product. The manufacturing process for MF betaine exhausts DMAPA. The levels of DMAPA and amidoamine were reported to be below 0.0002% (the detection limit) and <0.5%, respectively, in babassuamidopropyl betaine, coco/sunfloweramidopropyl betaine, isostearamidopropyl betaine, lauramidopropyl betaine, oleamidopropyl betaine, ricinoleamidopropyl betaine, and wheat germamidopropyl betaine.

The CIR accepts the US Food and Drug Administration (FDA) determination (21 CFR 700.27(a)) that tallow derivatives are not prohibited cattle materials.

Table 1. Definitions, Structures, and Functions for CAPB and Related Amidopropyl Betaine Ingredients[2]

Ingredient	Definition	Function	Related CIR Reviews and Conclusions
Cocamidopropyl Betaine (CAS Nos. 61789-40-0; 83138-08-3; 86438-79-1)	The zwitterion (inner salt) that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from coconut oil.	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Coconut oil & acid 1986, Safe; 2008 safe
Almondamidopropyl betaine (CAS no. not found)	The zwitterion (inner salt) that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from almond oil.	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Almond oil 1983, safe; 2005, not reopened
Apricotamidopropyl betaine (CAS no. 133934-08-4)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from *Prunus armeniaca* (apricot) kernel oil (qv)	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Avocadamidopropyl Betaine (CAS No. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from *Persea gratissima* (avocado) oil (qv)	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Avocado oil 1980, safe; 2003, not reopened
Babassuamidopropyl betaine (CAS no. 147170 44 3)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from *Orbignya oleifera* (Babassu) Oil.	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Behenamidopropyl Betaine (CAS no. 84082 44 0)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Canolamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from canola oil	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Capryl/capramidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from caprylic and capric acids	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Coco/oleamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from coconut oil	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Oleic acid 1987, safe; 2006, not reopened coconut oil & acid 1986, safe; 2008 safe
Coco/sunfloweramidopropyl betaine (CAS no. 147170 44 3)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from a blend of coconut and sunflower seed oils	Slip modifiers; surfactants cleansing agents; surfactants foam boosters; surfactants solubilizing agents; viscosity increasing agents aqueous	NA

(continued)

Table 1. (continued)

Ingredient	Definition	Function	Related CIR Reviews and Conclusions
Cupuassamidopropyl betaine (CAS no. 6573S0 94 2)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from the pulp of the cupuassu tree (*Theobroma grandiflorum*).	Hair-Conditioning Agents; Skin-Conditioning Agents Miscellaneous; Surfactants Cleansing Agents; Surfactants Foam Boosters; Viscosity Increasing Agents Aqueous	None
Isostearamidopropyl betaine (CAS no. 63566 37 0)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Isostearic acid 1983, safe; 2005, not reopened
Lauramidopropyl betaine (CAS nos. 4292 10 8; 86438 78 0)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Lauric acid 1987, safe; 2006, not reopened
Meadowfoamamidopropyl betaine (CA5 no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from meadowfoam seed oil	Humectants; skin protectants	None
Milkamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from milk	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Minkamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from mink oil	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Mink oil 2005, safe
Myristamidopropyl betaine (CAS no. 59272 84 3)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Myristic acid 1987, safe; 2006, not reopened; currently under reivew with the myristates group
Oatamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from *Avena sativa* (oat) kernel oil (qv)	Antistatic agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Oleamidopropyl betaine (CAS no. 25054 76 6)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Oleic acid 1987, safe; 2006, not reopened
Olivamidopropyl Betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from olive oil	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Palmamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from palm oil	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Palm oil 2000, safe

(continued)

Table 1. (continued)

Ingredient	Definition	Function	Related CIR Reviews and Conclusions
Palmitamidopropyl betaine (CAS no. 32954 43 1)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Palmitic acid 1987, safe; 2006, not reopened
Palm kernelamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from palm kernel oil	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Palm kernel oil 2000, safe
Ricinoleamidopropyl betaine (CAS no. 71850 81 2)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Ricinoleic acid 2005, safe
Sesamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from sesame oil	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Sesame seed oil 1993, safe; currently under review.
Shea butteramdiopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from *Butyrospermum parkii* (shea butter).	Surfactants cleansing agents; surfactants foam boosters	None
Soyamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from soy	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Stearamidopropyl betaine (CAS no. 6179 44 8)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Stearic acid 1987, safe; 2006, not reopened
Tallowamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from tallow	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Tallow 1990, safe; 2006, not reopened
Undecyleneamidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	None
Wheat germamidopropyl betaine (CAS no. 133934 09 5)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from wheat germ	Antistatic agents; hair-conditioning agents; skin-conditioning agents miscellaneous; surfactants cleansing agents; surfactants foam boosters; viscosity increasing agents aqueous	Wheat germ oil 1980, safe; 2003, not reopened

Table 2. Technical Names for CAPB and Related Amidopropyl Betaines[2]

Ingredient	Technical/Other Names
Cocamidopropyl betaine	CADG *N*-(carboxymethyl)-*N*,*N*-dimethyl-3-[(1-oxococonut)amino]-1-propanaminium Hydroxide, inner salt Cocamido betaine Cocamidopropyl dimethyl glycine Cocoyl amide propylbetaine Cocoyl amide propyldimethyl glycine Cocoyl amide propyldimethyl glycine solution 1-Propanaminium, *N*-(carboxymethyl)-N,N-dimethy-3-[(1-oxococonut)amino]-, hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3-cocoamidopropyl)dimethyl, hydroxides, inner salts
Almondamidopropyl betaine	Almond amide propylbetaine Almondamidopropyl dimethyl glycine *N*-(carboxymethyl)-*N*,*N*-dimethyl-3-[(1-oxoalmond)amino]-1-propanaminium hydroxide, inner salt 1-propanaminium, *N*-(carboxymethyl)-*N*,*N*-dimethyl-3-[(1-oxoalmond)amino]-, hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 almondamidopropyl) dimethyl, hydroxide, inner salt
Apricotamidopropyl betaine	Apricot amide propylbetaine Apricotamidopropyl dimethyl glycine *N* (carboxymethyl) *N*,*N* dimethyl 3 [(1 oxoapricot)amino] 1 propanaminium hydroxide, inner salt 1 propanaminium, 3 amino *N*(carboxymethyl) *N*,*N* dimethyl, N apricot oil acyl derivs, hydroxides, inner salts 1 propanaminium, *N* (carboxymethyl) *N*,*N* dimethyl 3 [(1 oxoapricot)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 apricotamidopropyl) dimethyl, hydroxide, inner salt
Avocadamidopropyl betaine	Avocado amide propylbetaine Avocadoamidopropyl dimethyl glycine *N*(carboxymethyl) *N*,*N* dimethyl 3 [(1 oxoavocado)amino] 1 propanaminium hydroxide, inner salt 1 propanaminium, *N*(carboxymethyl) *N*,*N* dimethyl 3 [(1 oxoavocado)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 avocadoamidopropyl) dimethyl, hydroxide, inner salt
Babassuamidopropyl betaine	Babassu amide propylbetaine Babassuamidopropyl dimethyl glycine *N* (carboxymethyl) *N*,*N* dimethyl 3 [(1 oxobabassu)amino] 1 propanaminium hydroxide, inner salt 1 propanaminium, *N* (carboxymethyl) *N*,*N* dimethyl 3 [(1 oxobabassu)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 babassuamidopropyl) dimethyl, hydroxide, inner salt
Behenamidopropyl betaine	Behenamide propylbetaine Behenamidopropyl dimethyl glycine 1 propanaminium, *N* (carboxymethyl) *N*,*N* dimethyl 3 [(1 oxobehenyl)amino], hydroxide, inner salt 1 propanaminium, *N*(carboxymethyl) *N*,*N* dimethyl 3 [(1 oxodocosanyl)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 behenamidopropyl) dimethyl, hydroxide, inner salt
Canolamidopropyl betaine	None found.
Capryl/Capramidopropyl betaine	None found.
Coco/oleamidopropyl betaine	None found.
Coco/sunfloweramidopropyl betaine	1 Propanaminium, 3 amino *N*(carboxymethyl) *N*,*N* dimethyl, *N* (C8 18 and C18 Unsatd. Acyl) derivs, hydroxides, inner salts
Cupuassuamidopropyl betaine	1 Propanaminium, 3 amino *N*(carboxymethyl) *N*,*N* dimethyl *N* (*Theobroma grandiflorum* acyl) Derivs
Isostearamidopropyl betaine	N (Carboxymethyl) N,N Dimethyl 3 [(1 Oxoisooctadecyl)Amino] 1 Propanaminium Hydroxide, Inner Salt 1 Propanaminium, N (Carboxymethyl) N,N Dimethyl 3 [(1 Oxoisooctadecyl)Amino], Hydroxide, Inner Salt
Lauramidopropyl betaine	Ammonium, (carboxymethyl)(3 lauramidopropyl)diemthyl, hydroxide, inner salt N (carboxymethyl) N,N dimethyl 3 [(1 oxododecyl)amino] 1 propanaminium hydroxide, inner salt N (dodecylamidopropyl) N,N diemthylammonium betaine Glycine, (3 lauramidopropyl)diemthylbetaine Lauroyl amide propyldimethyl glycine solution 1 propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxododecyl)Amino], hydroxide, inner salt
Meadowfoamamidopropyl betaine	None found.
Milkamidopropyl betaine	None found.

(continued)

Table 2. (continued)

Ingredient	Technical/Other Names
Minkamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxomink)amino] 1 propanaminium hydroxide, inner salt Mink amide propylbetaine Minkamidopropyl dimethyl glycine 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxomink)amino], hydroxide, inner salt Quaternary ammonium compounds, (carboxymethyl)(3 minkamidopropyl) dimethyl, hydroxide, inner salt
Myristamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxotetradecyl)amino] 1 propanaminium hydroxide, inner salt Myristamidopropyl dimethyl glycine 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxotetradecyl)amino], hydroxide, inner salt
Oatamidopropyl betaine	None found.
Oleamidopropyl betaine	Ammonium, (carboxymethyl)dimethyl(3 oleamidopropyl), hydroxide, inner salt N (carboxymethyl) N,N dimethyl 3 [(1 oxooctadecenyl)amino] 1 Propanaminium hydroxide, inner salt Oleamidopropyl dimethyl glycine 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxooctadecenyl)amino], hydroxide, inner salt
Olivamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxoolive)amino] 1 propanaminium hydroxide, inner salt Olivamidopropyl dimethyl glycine Olive amide propylbetaine 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxoolive)amino], hydroxide, inner salt
Palmamidopropyl betaine	Quaternary ammonium compounds (carboxymethyl)(3 oliveamidopopyl) dimethyl, hydroxide, inner salt None found.
Palmitamidopropyl betaine	Ammonium (carboxymethyl)dimethyl(3 palmitamidopropyl), hydroxide, inner salt *N* (carboxymethyl) *N,N* dimethyl 3 [(1 oxohexadecyl)amino] 1 propanaminium hydroxide, inner salt Pendecamaine (INN) 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxohexadecyl)amino], hydroxide, inner salt
Palm Kernelamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxopalm kernel)amino] 1 propanaminium hydroxide, inner salt Palm kernel amide propylbetaine Palm kernelamidopropyl dimethyl glycine Palm kernel oil amide propyl dimethyl glycine solution 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxopalm kernel)amino], hydroxide, inner salt Quaternary ammonium compounds, (carboxymethyl)(3 palm kernelamidopropyl) dimethyl, hydroxide, inner salt
Ricinoleamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxoricinoleyl)amino] 1 propanaminium hydroxide, inner salt 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxoricinoleyl)amino], hydroxide, inner salt Propyl betaine ricinoleate amide solution Ricinoleamidopropyl dimethyl glycine
Sesamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxosesame)amino] 1 propanaminium hydroxide, inner salt 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxosesame)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 sesameamidopropyl) dimethyl, hydroxide, inner salt Sesame amide propylbetaine Sesamidopropyl dimethyl glycine
Shea butteramidopropyl betaine	None found
Soyamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxosoy)amino] 1 propanaminium hydroxide, inner salt 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxosoy)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 soyamidopropyl) dimethyl, hydroxide, inner salt Soy amide propylbetaine Soyamidopropyl dimethyl glycine
Stearamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxooctadecyl)amino] 1 propanaminium hydroxide, inner salt 1 propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxooctadecyl)amino], hydroxide, inner salt Stearoyl amide propyl dimethyl glycine
Tallowamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxotallow)amino] 1 propanaminium hydroxide, inner salt 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxotallow)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 tallowamidopropyl)dimethyl, hydroxides, inner salts
Undecylenamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxoundecylenyl)amino] 1 propanaminium hydroxide, inner salt 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxoundecylenyl)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 undecylenamidopropyl) dimethyl, hydroxide, inner salt Undecylenamide propylbetaine Undecylenamidopropyl dimethyl glycine
Wheat germamidopropyl betaine	N (carboxymethyl) N,N dimethyl 3 [(1 oxowheat germ alkyl)amino] 1 propanaminium hydroxides, inner salts 1 Propanaminium, 3 amino N (carboxymethyl) N,N dimethyl, N wheat oil acyl derivs, hydroxides, inner salts 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxowheat germ)amino], hydroxide, inner salt

Table 3. Composition, Chemical, and Physical Characteristics of Batches of Cosmetic Grade CAPB[5]

Color	Clear pale yellow liquid
Odor	Faint
pH	4.6-5.6
Water content	62%-66%
NaCl	4.6%-5.6%
Active materials (100 - H2O - NaCl, %)	29.5%-32.5%
Alkalinity	0.725-0.825 Meq/g
Boiling point	230°F
Specific gravity	1.04
Solubility at 25°C	
Water	2 g/10 mL
Alcohol	2 g/10 mL
Fatty acids	
C8	5.6%-6.0%
C10	5.4%-5.7%
C12	53.1%-53.2%
C14	16.1%-17.4%
C16	8.1%-8.3%
C18	10.0%-10.2%

Impurities

No *N*-nitroso compounds were detected in samples of commercially supplied CAPB.[12] CAPB samples with and without internal standards of *N*-nitroso compounds were analyzed using gas chromatography with a thermal energy analyzer (TEA). The CAPB has a secondary amido group that is susceptible to *N*-nitrosation to form an *N*-nitrosamide. Although a highly sensitive analytical method failed to detect traces of volatile *N*-nitrosamines in samples of commercial CAPB, this result does not exclude the possibility that in the presence of *N*-nitrosating agents CAPB gives rise to reactive and unstable nitrosamides. The TEA method does not detect nitrosamides.[13]

Coconut oil impurities may be present in CAPB, depending on the degree of refining to which the coconut oil is subjected, including free fatty acids and low concentrations of sterols, tocopherol, squalene, and lactones. Concentrations of pigments, phosphatides, gums, and other nonglyceride substances are usually low in coconut oil in contrast to other vegetable oils.[14]

Impurities associated with CAPB are the reactants and intermediates from production and include amidoamine, sodium monochloroacetate, and DMAPA.[7,9,10] Depending on the manufacturer, residual amidoamine and DMAPA can range from 0.3% to 3.0% and from 0.0003% to 0.02%, respectively.[9]

In 2007, the Personal Care Products Council surveyed suppliers regarding the levels of DMAPA and amidoamine in CAPB. The limit of detection for DMAPA is 100 ppm in some analytical methods, but some methods may detect this impurity at concentrations as low as 2.5 ppm. Several companies reported DMAPA below the 100 ppm detection limit, with 1 supplier reporting a DMAPA below the limit of detection of 0.0002%. The survey found levels of amidoamine ranged from 0.5% to 5%, with 0.5% the typical value and 1.5% the suggested maximum level. The variability in the amidoamine levels may be due to the differences in analytical methods.[11,15]

Meadowfoam seed oil has been reported to have a typical value of <1 ppm for the heavy metal iron, copper, lead, mercury, cadmium, selenium, and chromium. The maximum value is 10 ppm.[16]

Use

Cosmetic

According to information supplied to the FDA by industry as part of the Voluntary Cosmetic Registration Program (VCRP), CAPB is used in a total of 2743 products (Table 5).[22] A use concentration survey conducted by the Council showed CAPB use at concentrations ranging from 0.005% to 11%.[23,24]

The VCRP also reported uses of babassuamidopropyl betaine, capryl/capramidopropyl betaine, coco/oleamidopropyl betaine, lauramidopropyl betaine, oatamidopropyl betaine, olivamidopropyl betaine, soyamidopropyl betaine, and undecylenamidopropy betaine, with the highest total of uses reported for lauramidopropyl betaine at 187.[22] Concentration of use ranges was reported for almondamidopropyl betaine, babassuamidopropyl betaine, capryl/capramidopropyl betaine, lauramidopropyl betaine, myristamidopropyl betaine, oatamidopropyl betaine, palm kernelamidopropyl betaine, shea butteramidopropyl betaine, soyamidopropyl betaine, and undecylenamidopropyl betaine, with the highest concentration of use reported for lauramidopropyl betaine at 13%.[23] For complete information on these ingredients, see Table 5. No uses or concentrations of uses were reported for: apricotamidopropyl betaine, avocadamidopropyl betaine, behenamidopropyl betaine, canolamidopropyl betaine, coco/sunfloweramidopropyl betaine, cupuasuamidopropyl betaine, isostearamidopropyl betaine, MF betaine, milkamidopropyl betaine, minkamidopropyl betaine, oleoamidopropyl betaine, palmamidopropyl betaine, palmitamidopropyl betaine, ricinoleamidopropyl betaine, sesamidopropyl betaine, stearamidopropyl betaine, tallowamidopropyl betaine, and wheat germamidopropyl betaine.

The CAPB is primarily used as a pseudoamphoteric surfactant in hair shampoos.[1] Gottschalck and Bailey described the current functions of CAPB as antistatic agent; hair-conditioning agent; skin-conditioning agent—miscellaneous; surfactant-cleansing agent; surfactant-foam booster; and viscosity increasing agent—aqueous.[2]

The CAPB is used in hair sprays and other spray products, and effects on the lungs that may be induced by aerosolized products containing this ingredient are of concern.

There are no specific data for spray products containing CAPB. Jensen and O'Brien reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.[25] The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is

Table 4. Fatty Acid Compositions of the Oil Components of Amidopropyl Betaines (%)[16-21]

Fatty Acids	Coconut	Almond	Apricot	Avocado	Babassu	Canola	Cupuassu	Meadowfoam Seed
Caproic (C6)	0.008-1.2							
Caprylic (C8)	3.4-15				4-8			
Capric (C10)	3.2-15				4-8			
Lauric (C12)	41-51.3				44-47			
Myristic (C14)	13-23				15-20			
Palmitic (C16)	4.2-18	5.5-6.5	Small quantities	13-17	6-9	2.8-3	5.8	
Stearic (C18)	1.6-4.7	2-3			3-5	1.3	38.3	
Oleic (C18:1)	3.4-12	70-77		67-72	10-12	57.1-57.4	42.8	
Oleic/Linoleic			90-93					
Linoleic (C18:2)	0.9-3.7	17-20		10-12	1-3	20.1-22.1		
Arachidic (C20)	1.03						4.8	
Palmitoleic (C16:1)				3-5.1				
Linolenic (C18:3)						10.8-12.5	8.3	
Eicosenoic (C20:1)						2.5-3.1		52-77[a]
Erucic (C22:1)						1-3.3		8-29[a]
C22:2								7-20[a]

[a]Natural Plant Products, Inc, reports the fatty acid composition of meadowfoam seed oil to be 58%-64% C20:1 (♠5), 3%-6% C22:1 (♠5), 10%-14% C22:1 (♠13), and 15%-21% C22:2 (♠5♠13).

Table 4. Fatty Acid Compositions of the Oil Components of Amidopropyl Betaines (%) (Continued)[16-21]

Fatty Acids	Mink Crude	Olive	Palm	Palm Kernel	Sesame	Shea	Soybean	Sunflower	Tallow	Wheat Germ
Caprylic (C8)				3%-4%						
Capric (C10)				3-7%						
Lauric (C12)	0.1			46%-52%						
Myristic (C14)	3.5		1-6	15%-17%					3-6	
Myristoleic (C14:1)	0.9									
Pentadecanoic (C15)	0.1									
Palmitic (C16)	17.2	7.5-20	32-47	6%-9%	7%-10.9%	5-9		5.2-7.2	24-32	11-16
Heptadecanoic (C17)	0.4									
Heptacdecanoic (C17:1)	0.5									
Stearic (C18)	2.5	0.5-3.5	1-9	1-3%	3.4-6%	30-41		2.7-6.5	20-25	1-6
Oleic (C18:1)	40.9	53-86	39-53	13%-19%	32.7%-53.9%	45-50	11.5-60	14.7-35	37-43	8-30
Linoleic (C18:2)	15.0	3.5-20	2-11	0.5-2%	37-59%	4-5	25-63.1	51.5-73.5	2-3	44-65
Arachidic (C20)					0.3%-8%			0.3-1		
Palmitoleic (C16:1)	17.0	0.3-3.5								
Linolenic (C18:3)	0.6	0-1.5					2.9-12.1	0.01-0.3		4-10
Eicosenoic acid (C20:1)										
Eicolenoic (C20:1)	0.6									
Other							12-13.5 (unknown saturated acids)			0-1.2 (C20-C22 saturated acids)
Cholesterol, arachidonic acid, elaidic acid, and vaccenicacid									5mall quantities	

the aerodynamic diameter, d_a, defined as the diameter of a sphere of unit density possessing the same terminal setting velocity as the particle in question. These authors reported a mean aerodynamic diameter of 4.25 $\pm$ 1.5 μm for respirable particles that could result in lung exposure.[25]

Bower reported diameters of anhydrous hair spray particles of 60 to 80 μm and pump hair sprays with particle diameters of $\geq$80 μm.[26] Johnsen reported that the mean particle diameter is around 38 μm in a typical aerosol spray.[27] In practice, he stated that aerosols should have at least 99% of particle diameters in the 10 to 110 μm range.

The CAPB was not restricted from use in any way under the rules governing cosmetic products in the European Union.[28]

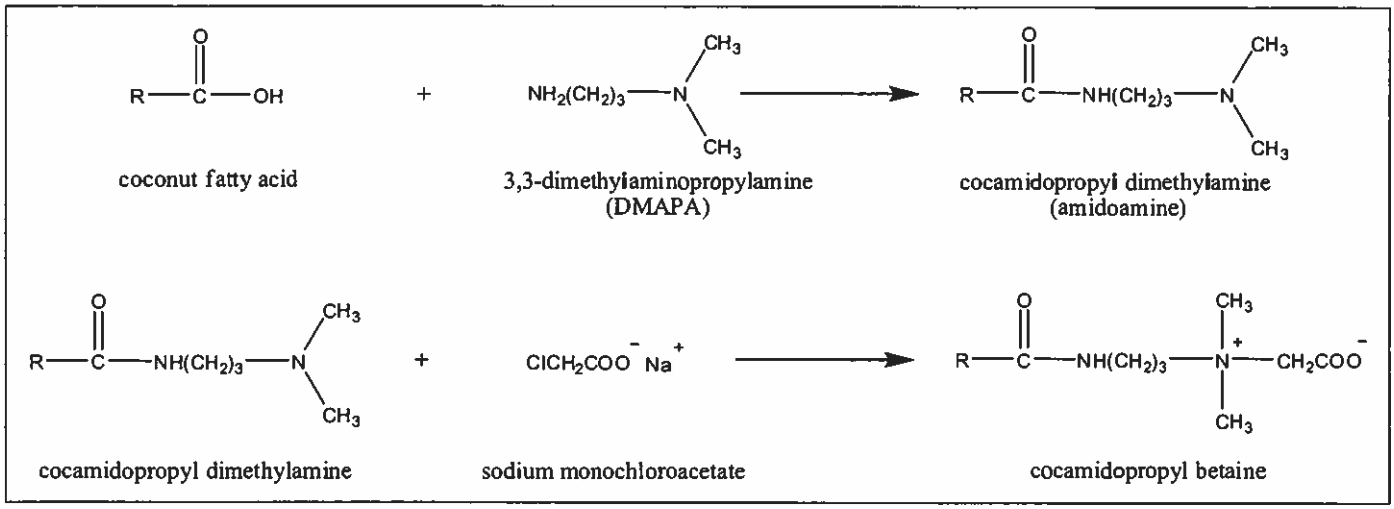

Figure 2. Reaction process of cocamidopropyl betaine (R represents the coconut fatty acid chain that varies between C-8 and C-18).

Noncosmetic

The CAPB is used in household cleaning products, including laundry detergents, hand dishwashing liquids, and hard surface cleaners.[29] A 30% active CAPB solution was tested for antibacterial and antimycotic activity using the agar cup plate method.[30] Zones of inhibition were measured for the bacteria and molds around agar cups containing 0.2 mL of the ingredient, which had been diluted with distilled water to 0.5% activity. No inhibition against *Escherichia coli* or *Pseudomonas aeruginosa* was observed. Bacteriostatic activity was detected in cultures of *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Bacillus subtilis*. Fungicidal activity was observed in cultures of *Candida albicans*, *Trichophyton mentagrophytes*, and *Pityrosporum ovale*.

Toxicokinetics

No studies were found on the absorption, distribution, metabolism, and excretion of CAPB or other amidopropylbetaines. It is unclear whether the amide bond can be hydrolyzed to yield the fatty acids and 3-aminopropyl betaine. No metabolism data are available on the latter compound.

Toxicological Studies

Single-Dose (Acute) Toxicity

Oral. A full-strength CAPB solution, 30% active, was administered by gastric intubation to groups of 10 CFR mice of the Carworth strain, weighing 18 to 21 g. Mice were observed for 7 days following the administration. The oral LD_{50} was 6.90 g/kg (calculated from volume per weight dosage units, based on a density of 1.07 g/mL). Confidence range is 6.06 to 7.86 g/kg.[31]

Undiluted CAPB, 30% active, with a pH of 5.5, was administered by gavage to groups of 10 (5 female, 5 male) Wistar rats.[32] Dosage groups were 5.00, 6.30, 7.94, and 10.00 mL/kg. The rats were observed for 14 days. The oral LD_{50} was 7.97 g/kg (calculated from volume per weight dosage units, based on a density of 1.07 g/mL). Confidence range is 6.93 to 9.17 g/kg. Rats in all dosage groups had decreased motor activity, abnormal body posture, coordination disturbance, cyanosis, diarrhea, and decreased body temperature beginning approximately 20 minutes after dosage and persisting for 24 hours. Surviving rats in all groups had body weight gains of 36 to 45 g and were normal in appearance and behavior. Redness of the stomach and intestinal mucous membranes were observed at necropsy.

A full-strength solution of CAPB, 30% active, was administered by gavage to groups of 5 albino rats at single doses of 2.0, 4.0, 5.0, 6.3, 8.0, and 16.0 g/kg, and the rats were observed for 14 days.[33] Sluggishness, nasal hemorrhaging, diarrhea, and wetness around the hindquarters were observed, increasing in severity with dosage. The oral LD_{50} for this full strength, 30% active CAPB solution was estimated at 4.9 g/kg, with a 95% confidence limit of 3.7 to 6.5 g/kg.

A full-strength solution of CAPB, 30% active, was administered by gavage to groups of 10 (5 female, 5 male) Sprague-Dawley rats at single doses of 2.0, 2.71, 3.68, 5.0, or 6.78 g/kg, and the rats were observed for 15 days.[34] At necropsy, a blood-like, viscous liquid was found in the intestines. Surviving rats gained an average between 20 and 130 g by day 15. Diarrhea was observed in rats of all treatment groups, and decreased motor activity was observed in rats of all treatment groups, except at the lowest dose. Dried blood around the nose and salivation were observed in male rats of the 5.0 g/kg dosage groups. The acute oral LD_{50} for this full-strength CAPB, 30% active, was 4.91 g/kg within 95% confidence limits of 4.19 to 5.91 g/kg.

The American Chemistry Council summarized an acute oral toxicity study on 35.61% active CAPB.[35] Fasted Sprague-Dawley rats (5 female, 5 male; 220-294 g) received a single, oral dose via gavage of undiluted test material. The rats were weighed before dosing and at study termination, and they were observed frequently from the day of dosing and for 14 days. Animals that died during the study underwent gross necropsy. All of the female rats died on day 2 of the study. Prior to death,

Table 5. Current Cosmetic Product Uses and Concentrations for Cocamidopropyl Betaine and Its Related Amidopropyl Betaine According to Duration and Exposure[22,23]

	Cocamidopropyl Betaine		Almondamidopropyl Betaine		Babassuamidopropyl Betaine		Capryl/Capramido-propyl Betaine		Coco/Oleamidopro-pyl Betaine		Lauramidopropyl Betaine		Myristamidopropyl Betaine	
	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)
Totals	3287	0.005-11	NR	3	25	0.9-4	3	0.3-2	10	NR	227	0.00006-13	1	0.3
Duration of use														
Leave-on	*228*	*0.2-6*	NR	NR	NR	NR	2	2	4	NR	9	0.00006-6	NR	NR
Rinse off	*3059*	*0.005-11*	NR	3	25	0.9-4	1	0.3	6	NR	218	0.6-13	1	0.3
Exposure type														
Eye area	*8*	0.005-3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Possible ingestion	NR	0.6-6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Inhalation	24	0.2-6	NR	NR	NR	NR	NR	NR	NR	NR	NR	4	NR	NR
Dermal contact	1859	0.005-11	NR	3	9	0.9-2	2	2	9	NR	148	0.7-13	NR	0.3
Deodorant (underarm)	NR	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair—nonColoring	1000	0.2-9	NR	NR	15	0.9-4	1	0.3	1	NR	48	0.00006-8	1	NR
Hair—coloring	426	0.6-6	NR	NR	1	NR	NR	NR	NR	NR	28	0.6	NR	NR
Nail	1	0.8	NR	NR	NR	NR	NR	NR	NR	NR	3	NR	NR	NR
Mucous membrane	1252	0.5-10	NR	NR	4	2	NR	NR	3	NR	87	2-13	NR	NR
Bath products	180	0.06-7	NR	NR	NR	NR	NR	NR	NR	NR	12	3-8	NR	NR
Baby products	106	2-6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviation: NR, not reported to the VCRP or Council; VCRP, Voluntary Cosmetic Registration Program.

Table 5. Current Cosmetic Product Uses and Concentrations for Cocamidopropyl Betaine and Its Related Amidopropyl Betaine According to Duration and Exposure (Continued)[22,23]

	Oatamdiopropyl Betaine		Olivamidopropyl Betaine		Palm Kernelamidopropyl Betaine		Shea Butteramidopropyl Betaine		Soyamidopropyl Betaine		Undecylenamidopropyl Betaine	
	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 2010	Conc. of Use 2010 (%)
Totals	1	0.3	1	NR	NR	0.9-5	11	0.6-4	4	1-2	1	2
Duration of use												
Leave-on	1	0.3	NR	NR	NR	NR	NR	NR	1	NR	NR	NR
Rinse off	NR	NR	1	NR	NR	0.9-5	11	0.6-4	3	1-2	1	2
Exposure type												
Eye area	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Possible ingestion	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dermal contact	1	0.3	1	NR	NR	0.9	9	0.6-4	4	2	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR	NR	5	2	NR	NR	1	1	2
Hair—coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	0.9	9	2	NR	NR	NR	NR
Bath products	NR	NR	NR	NR	NR	NR	NR	0.6	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviation: NR, not reported to the VCRP or Council; VCRP, Voluntary Cosmetic Registration Program.

the females exhibited salivation, diarrhea, ataxia, and/or decreased activity. Male rats exhibited similar clinical signs on day 1 (day of dosing) and day 2 but had recovered by day 3. Necropsy data were not reported. The acute oral LD_{50} for 35.61% active CAPB was >1.8 g/kg for male rats.

The CAPB (31% active) was orally administered to male and female CD rats (5/sex; 110-150 g) at 5.0 g/kg body weight via gavage. Animals were observed daily until 14 days after dosing and were killed on day 15. Individual body weights were recorded on days 1, 8, and 15. Macroscopic postmortem examinations performed. Clinical signs of toxicity included piloerection, increased salivation, hunched posture, and diarrhea. Animals recovered by day 4. Slightly reduced body weight gains were recorded for 4 males and 3 females on day 8, but all animals achieved expected weight gains by day 15. No abnormalities were observed at necropsy. The acute oral LD_{50} was greater than 5.0 g/kg.[35]

In another acute oral toxicity study reported by the American Chemistry Council, fasted Wistar rats (5 rats per dose, sexes combined; 200-300 g) received a single oral gavage dose of CAPB (30% aqueous) at levels of 4.0, 8.0, 10.0, 12.5, 16.0, or 32.0 g/kg.[35] The rats were observed daily for 2 weeks after dosing. No postmortem or histopathology examinations were performed. Clinical signs included slight diarrhea and unkempt coats in the 4.0 g/kg dose group, and lethargy, diarrhea, nasal hemorrhage, and unkempt coats was observed in the dose group of 8.0 g/kg and above, with severity increasing proportionately. The acute oral LD_{50} was 8.55 g/kg. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 30% active or 30% aqueous, which equated to 9% active.)

Dermal

The American Chemistry Council summarized an acute dermal toxicity study of CAPB (31% active) using male and female CD rats (5/sex; 200-232 g).[35] The animals received 2.0 g/kg body weight on the clipped surface of the dorsolumbar region. The treated area was occluded. After 24 hours, the dressings were removed and the treated area was washed with warm water and blotted dry. The treated areas were examined daily for 14 days for signs of dermal irritation. The rats were weighed on days 1, 8, and 15. At day 15, the rats were necropsied. No unscheduled deaths occurred and no clinical signs of systemic toxicity were observed. No abnormalities were observed at necropsy. Slight or well-defined erythema was observed on day 2, with well-defined erythema persisting in 3 males and all females on day 3 and completely resolving by day 6. Sloughing or hyperkeratinization affected 6 rats on days 4 and 5 only. The acute lethal dermal dose of CAPB (31% active) was greater than 2.0 g/kg.

Repeated Dose Toxicity

Oral. Male and female Sprague-Dawley rats (8/sex/group) were treated with a full-strength (30.6% active) CAPB solution.[36] Three dose groups (100, 500, and 1000 mg/kg body weight) were given the test material by gavage for at least 28 days. A control group of 16 animals received deionized water. Rats dying during the study and those killed on completion of dosing were necropsied, and tissues were collected for histopathological evaluation.

Mortality was increased in the treated groups as compared to controls, but mortality did not follow a dose–response relationship. The principal necropsy finding in the rats that died was congestion, noted in several tissues, with additional alterations in the lungs of some rats. The death of a high-dose female was ascribed to a dosing accident. It was considered possible that the 1 death of a male of the low-dose group and 1 female of the mid-dose group could be attributed to dosing accidents. The other deaths were related to compound administration. This conclusion was supported by the observation that deaths occurred later (3-4 weeks of study in the mid-dose group, as compared to the high-dose groups: deaths at 1-2 weeks of study). However, doubling of the dose of compound (from 500 to 1000 mg/kg) did not increase mortality, so a dose–response relationship with the mortality was not evident.

Lesions (subacute inflammation and epithelial hyperplasia) of the nonglandular portion of the stomach were suggestive of irritation by CAPB. Lesions were found in 1 of 5 stomachs examined from the high-dose males and in all 7 from high-dose females. The loss of 3 males during the first 2 weeks of dosing prevented adequate evaluation of the response of male rats to the compound. Both males and females of the 100 mg/kg dose group were comparable to concurrent controls.

The American Chemistry Council summarized a 28-day short-term oral toxicity of CAPB (concentration not stated) in Sprague-Dawley rats.[35] Male and female rats received 0, 250, 500, or 1000 mg/kg body weight of the test material once daily via oral gavage on 5 consecutive days per week. The number distribution of the rats per group was not described.

No treatment-related deaths or decreases in feed or water consumption were observed over the course of the study. Hematological evaluations, clinical chemistry, ophthalmic examinations, and absolute and relative organ weights also did not find any treatment-related effects. Head protrusion at the beginning of week 3 and salivation at the beginning of week 4 were observed in the 1000 mg/kg dose group. Compound-related edema of the mucosa of the nonglandular stomach was observed at macroscopic examination in the 1000 mg/kg dose group, which disappeared in the rats in the recovery group. Microscopic examination of the rats in the 1000 mg/kg dose group found acanthosis of the gastric mucosa, inflammatory edema of the submucosa, and multiple ulcerations. Effects were greater in the females than the males. These effects were considered to be the result of the irritating properties of CAPB and not of systemic toxicity, especially since the 1000 mg/kg recovery animals had complete and regular regeneration of the nonglandular mucosa. No other treatment-related effects were observed in the organs. The study concluded that the NOEL was 500 mg/kg per d and the LOEL was 1000 mg/kg per d for exposure to CAPB in this rat study.

Groups of 10 male and 10 female Crl:CF(SD)BR Sprague-Dawley rats received 0, 250, 500, or 1000 mg/kg per d CAPB (concentration not stated) in distilled water once daily via oral gavage at a dose volume of 10 mL/kg per d for 92 days.[35] Clinical signs were recorded daily and body weight and feed consumption were recorded once weekly. Ophthalmic examinations were performed on the control and 1000 mg/kg per d dose groups prior to dosing and to all groups during the final week of treatment. Blood and urine samples were collected from all rats during the final week of treatment. Complete necropsy was performed on surviving rats at study termination. Histopathology was performed on select tissues from the rats in the control group and the 1000 mg/kg per d dose group. Because treatment-related histopathological changes were observed in the stomachs of the 1000 mg/kg per d group, stomachs from the 250 and 500 mg/kg per d groups also were examined microscopically.

No treatment-related deaths or effects were observed during the course of the study for either sex. Necropsy revealed stomach ulcers at the fundic and cardiac regions in 1 male and 1 female in the high-dose group. Microscopic evaluations found nonglandular gastritis in 6 male and 3 female rats in the 1000 mg/kg per d group, and in 2 male and 2 female rats in the 500 mg/kg per d group. This effect was not observed in the 250 mg/kg per d dose group. No other treatment-related effects were observed. The study concluded that the NOEL for this subchronic study of CAPB in rats was 250 mg/kg per d.

Dermal Irritation

Animal. The available data on skin irritation studies are summarized in Table 6.[37-43] These studies demonstrated that, while a full-strength CAPB solution, 30% active, was a mild irritant, a 50% dilution was nonirritating.

Human

Cocamidopropyl betaine. In a study of cumulative irritation, 0.3 mL of 2 soap formulations were applied to skin sites on the backs of 10 panelists using occlusive patches.[37] Each formulation contained 1.9% active CAPB. Daily 23 hour patches were applied for 21 consecutive days. The total irritation scores for all participants for all 21 applications of the 2 formulations were 588 and 581 (max 630), which indicated that these test formulations were primary irritants. The average irritation times for the formulations were 1.48 and 1.69 days, and the median irritation time was 2 days.

The CAPB at 0.06% (1.0% aqueous dilution of a product formulation containing 6.0% active CAPB) was tested for skin irritation using a single insult occlusive patch test and 19 panelists.[1] Fifteen panelists had no irritation and a + score was recorded for 4 panelists. The formulation was considered practically nonirritating.

Daily doses of 0.2 mL of 0.52% CAPB (an 8% aqueous dilution of a liquid soap formulation containing 6.5% active CAPB) were applied via occlusive patches to the forearms of 12 human participants for 5 days.[1] An erythema score of 0.48 (scale 0-4) was calculated.

Wheat germamidopropyl betaine. The irritation potential of 0.005% active wheat germamidopropyl betaine (a 0.5% aqueous solution of 1.0% wheat germamidopropyl betaine in a body polisher) was evaluated against a control shower gel in a single 24-hour insult patch test. Twenty participants completed the study. Two panelists had a $\pm$ score and 4 panelists had a 1 score and the primary irritation index (PII) was calculated at 0.25. The control substance elicited a $\pm$ score in 4 panelists, a 1 score in 2 panelists, and a + score in 2 panelists, yielding a PII of 0.35. The authors concluded that the test material containing 1.0% wheat germamidopropyl betaine was milder than the reference control.[38]

Dermal Sensitization

Animal. Delayed contact hypersensitivity of 15 male Pirbright white guinea pigs (400 $\pm$ 50 g) to a commercial 10% active sample of CAPB was examined using a maximization test.[39] Test animals were administered 0.1 mL of a 50% aqueous solution of Freund complete adjuvant at the first pair of sites on the clipped, dorsoscapular region, 0.1 mL of 0.5% (v/v) dilution of the CAPB (0.05% active CAPB) sample in sterile isotonic saline at the second pair of sites, and 0.1 mL of 0.5% (v/v) dilution of the CAPB (0.05% active CAPB) sample in a 1:1 mixture of isotonic saline and Freund complete adjuvant at the third pair of sites. One week following the injections, a single occlusive 48-hour induction patch of 60% (v/v) dilution of the CAPB (6% active CAPB) sample in distilled water was applied to the same shaved interscapular area. Five control animals received intradermal injections and induction patches without the CAPB solution. All animals received a single occlusive 24-hour challenge patch of 10% (v/v) dilution of the CAPB (1% active CAPB) sample in distilled water on the left flank 2 weeks after the induction.

Well-defined irritation was observed at all sites receiving intradermal injections of Freund adjuvant. Temporary slight irritation was observed following injections of the 0.5% CAPB sample dilution in all test animals. Topical application of the 60% CAPB sample dilution resulted in slight dermal reactions. The barely perceptible erythema observed on the skin of 2 test animals after 24 hours was considered unrelated to CAPB treatment but was attributed to reactions to the elastic adhesive bandages used for site occlusion. With the exception of slight reactions to the bandages, no reactions were observed in controls throughout the 72-hour observation period. No evidence of delayed contact hypersensitivity was found.

A formulation containing 0.75% active CAPB was tested in a delayed contact hypersensitivity test.[40] Closed patches containing 0.4 mL of the test solution were applied to the shaved area on the left shoulder of 20 albino guinea pigs. After 6 hours, the patch was removed and the area was rinsed with warm water. This procedure was repeated at the same site for the following 2 weeks. The animals were left untreated for 2 weeks

Table 6. Animal Skin Irritation Studies on CAPB

Concentration	Number and Species	Results	References
50%, Diluted 1 part + 1 part (v/v)	3 albino rabbits	No erythema, eschar, or edema; not a primary skin irritant.	44
30% Active[a]	6 Albino rabbits	PII = 0.5. Very slight to well-defined erythema, no edema; mild primary irritant.	45
7.5% Active[a] solution	3 Albino rabbits	No irritation.	46
10% Active[a] solution, pH 6.1	1 Albino rabbit	PII = 0.25; nonirritating.	47
10% Active[a] solution, pH 4.5	6 NZW rabbits	PII = 0.3. Very slight erythema, no edema.	48
30% Active[a]	6 NZW rabbits	PII = 3.75. Eschar formation.	49
15% Active[a] solution	3 Albino rabbits	PII = 3.5. Well-defined erythema, slight edema; not a primary skin irritant.	50

[a] Referenced as full strength.

before the primary challenge test, which used 0.01875% CAPB (a 2.5% solution of the 0.75% active CAPB) applied to a freshly clipped skin site not previously treated for 6 hours. Responses were graded after 24 and 48 hours. There was no evidence of sensitization following the exposure to the 3 dermal treatments or challenge dose.

A full-strength, 30% active CAPB sample was tested for skin sensitization using a maximization test and a modified Draize test.[41] Albino guinea pigs (20 animals) received intradermal injections of (1) Freund complete adjuvant alone, (2) 0.1% aqueous dilution of the CAPB sample (0.03% active CAPB), and (3) 0.1% aqueous dilution of the CAPB sample (0.03% active CAPB) plus the adjuvant. One week later, a topical 48-hour occlusive induction patch containing the 10% aqueous dilution of the CAPB sample (3% active CAPB) was applied. Animals in the control group received intradermal injections and topical application of water alone. After 3 weeks, single 24-hour occlusive patches were applied to the clipped flanks of all animals. A 10% aqueous dilution of the CAPB sample (3% active CAPB) was applied to the left flank, and water was applied to the right. The lesions at necropsy were erythema and edema in 8 of the 20 test animals after the challenge application. Microscopic findings included epidermal acanthosis, inter- and intracellular edema, and massive infiltration of the superficial layers of the dermis with lymphocytes, monocytes, and a few eosinophils with a tendency to invade the epidermis in 2 of the animals. Less prominent microscopic lesions of acanthosis, mild intracellular edema, and a moderate lymphomononuclear infiltrate in the superficial dermis were found in 4 additional animals. Slight acanthosis was observed in the remaining 2 animals.

This same laboratory also tested 0.15% active CAPB for induction (0.015% for challenge) using the same assay. Slight erythema and edema were observed macroscopically in 6 of the 20 test animals. Slight acanthosis was observed microscopically. Control animals in the maximization and modified Draize tests had no dermatitis-type clinical or histological alterations. A few controls had moderate acanthosis with edema and vasodilation in the subjacent papillary layer of the dermis. The investigators concluded that the commercially supplied CAPB is capable of producing a delayed-type contact sensitization.

Basketter et al reported that CAPB was positive for sensitization in a local lymph node assay (LLNA).[42] The EC_3 value was not reported.

Dermal Sensitization

Fisher contact dermatitis recommended that patch testing with CAPB should be performed at a concentration of 1% aqueous.[43] Care was advised for patch test readings since mild false-positive irritant reactions may occur.

de Groot, in a review of contact allergy literature, stated that CAPB in rinse off products such as shampoo, shower gel, bath foam, and liquid soap was linked to cosmetic allergy.[7] Because patch testing for sensitization with these products may result in both false-positive and false-negative reactions, the author suggested that CAPB should be tested separately. The author also suggested that CAPB should be included in the hairdresser's series and the cosmetic series with the knowledge that commercial concentration of CAPB (1% in water, possibly 0.3% active) is a marginal irritant and not all positive patch test reactions indicate contact allergy to CAPB.

Another review of contact allergy literature by Mowad described CAPB as "contact allergen of the year" for 2004.[10] Because impurities in CAPB may be responsible for allergic reactions, the author advised patch testing for amidoamine and DMAPA along with CAPB. The author further suggested that patients that test positive to amidoamine or DMAPA should be advised to avoid products that contain CAPB.

Historically, sensitization study results are reported as positive/negative for a particular concentration of the chemical tested. More recently, the dose per unit area is considered as the relevant parameter.[51] CIR has performed calculations to determine dose per unit area where sufficient information was available.

The available data on clinical sensitization studies are summarized in Table 7.

Cocamidopropyl betaine. A repeated open application procedure was performed with 1.872% CAPB (a 10% w/v aqueous dilution of a shampoo containing 18.72% active CAPB), using 88 human volunteers to determine skin sensitization. [Estimated dose/unit area = concentration × amount × density × unit conversion × area^{-1} = 2.6 × 10^3 μg/cm^2]. The disk was removed after 10 minutes. Induction applications were made 3× a week for 3 weeks. Challenge patch strips were applied simultaneously to both the induction arm and the alternate arm,

Table 7. Clinical Sensitization Studies on CAPB and Related Amidopropyl Betaines.

Exposure	Subjects	Study Type	Result	Reference
Cocamidopropyl Betaine				
0.1872% active CAPB in a shampoo	88	Open application HRIPT	No sensitization	52
0.93% active ueous sol. of CAPB	93	Open application HRIPT	No sensitization	53
0.3% active CAPB in formulation	100	HRIPT	No sensitization	54
1.5% active ueous CAPB changed to 3.0% active CAPB	141	HRIPT	No sensitization	55
6% active CAPB in a cleansing cloth	210	HRIPT	No sensitization	56,57
0.018% active CAPB in a facial cleanser	27	HRIPT	No sensitization	58
1% aqueous CAPB or 0.3% active aq. CAPB	781	Patch test	56 positive (7.2%)	59
1% aqueous CAPB or 0.3% active aqueous CAPB	10,798	Patch test	29 positive (0.27%)	60
unknown % CAPB	12	Patch test	Irritation only	61
1% aqueous CAPB or 0.3% active aqueous CAPB	93	Patch test	4 positive reactions	62
1% aqueous CAPB or 0.3% active aqueous CAPB	210	Patch test	12 positive (5.75%)	63
Almondamidopropyl betaine and olivamidopropyl betaine				
1% active almondamidopropyl betaine and 1% active olivamidopropyl betaine in a body cleanser	103	HRIPT	No sensitization	64
Capryl/capramidopropyl betaine				
1.72% active capryl/capramidopropyl betaine in mousse with SLS cotreatment	26	Maximization test	No sensitization	65
Lauramidopropyl betaine				
14% active lauramidopropyl betaine in a shower gel with SLS co-treatment	25	Maximization test	No sensitization	66
0.042% active lauramidopropyl betaine in a shampoo	51	HRIPT	No sensitization	67
0.03955% active aq sol. of lauramidopropyl betaine in a body cleanser	109	HRIPT	No sensitization	68
Shea Butteramidopropyl Betaine				
0.54% active shea butteramidopropyl betaine in a body wash	25	Maximization test	No sensitization	69
0.04% active aq. sol. of shea butteramidopropyl betaine in a body scrub	101	HRIPT	No sensitization	68

positioned between the shoulder and elbow, 18 days after the last induction application. The areas were scored 24, 48, and 72 hours following the removal of the patch after a 6-hour period. The same procedures were performed with another test substance containing an identical concentration of CAPB. No sensitization was seen in any of the 88 participants exposed to either of the test materials.[52]

Another study was performed with a 0.93% active aqueous solution of CAPB. [Estimated dose/unit area = 7.7×10^2 μg/cm^2].[53] Ninety-three volunteers completed the study. Induction applications were made to the same site unless reactions became so strong that a first or second adjacent site had to be used for complete induction, and the sites were scored following a 48-hour period. An alternate site was used for the challenge test and was scored after 48 and 96 hours. Ten participants had slight responses to the test material. These responses were attributed to primary irritation, rather than sensitization, during both the induction and challenge tests.

In a similar study by Hill Top Research, Inc, a formulation containing 0.3% active CAPB was tested on 100 human volunteers.[54] The study had started out with CAPB at 0.6%, but due to several incidences of mild to moderate skin irritation early in the induction phase, the formulation was diluted. [Estimated dose/unit area = 2.5×10^2 μg/cm^2 at 0.3%]. No evidence of sensitization was observed in the formulation at 0.3% active CAPB.

CAPB was studied using 141 human participants. All applications contained a concentration of 1.5% active CAPB in distilled water, until a protocol modification changed the concentration to 3.0% active CAPB. Participants who began the study a week earlier received 2 applications at a concentration of 1.5%, and all other applications of the test material at a concentration of 3.0%. [Estimated dose/unit area = 5.8×10^1 μg/cm^2 at 1.5%, 1.2×10^2 μg/cm^2 at 3%]. Induction applications were made to the same, previously untreated site on the back 3 times per week for 3 successive weeks. Patches were removed after 24 hours. Following a 10- to 15-day nontreatment period, the challenge application was applied to a previously untreated site for 24 hours, and the site was scored 24 and 72 hours after patch removal. No responses were observed during either the induction or challenge tests.[55]

Clinical Research Laboratories, Inc performed an RIPT study on 6% active CAPB in cleansing cloths in 2 groups of participants (in phase I, 104 participants completed the study. In phase II, 106 participants completed the study).[56,57] The test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material was cut to a ½ inch square and applied to the upper back under a semioccluded patch for 24 hours. There were a total of 9 induction patches. Induction sites were scored for irritation. Following a 2-week rest period, challenge patches were applied to a virgin site on the back. After 24 hours, the patches were removed and evaluated for dermal reactions. The test sites were scored again at 48 and 72 hours. No reactions were observed in either group of participants. It was concluded that 6% active CAPB in cleansing cloths did not demonstrate a potential for eliciting dermal irritation or sensitization.

In a study by KGL, Inc, 0.018% active CAPB (a 0.5% aqueous dilution of a facial cleanser containing 3.6% active CAPB) was tested on 27 participants to determine skin sensitization.[58] In the induction phase, the participants were pretreated with 0.05 mL of 0.25% aqueous sodium lauryl sulfate (SLS) under an occluded 15 mm Webril disc for 24 hours on the upper outer arm, volar forearm, or back. After 24 hours, the SLS patch was removed and 0.05 mL of the test material was applied to the same site and occluded. The induction patch was left in place for 48 hours and the site was scored for irritation. [Estimated dose/unit area = 5.1 $\mu g/cm^2$]. If no irritation was present, the SLS patch followed by the test material patch procedure was repeated for a total of 5 induction exposures. If irritation developed at any time during the induction phase, the SLS treatment patch was eliminated and only the test material was reapplied after a 24-hour rest period. Following a 10-day rest period, the participants received 0.05 mL of 5% SLS for 1 hour prior to receiving the challenge patch of the test material to the opposite side of the body. The challenge patch was occluded and left in place for 48 hours. After patch removal, the site was scored 15 to 30 minutes later and again at 24 hours. No reactions were observed during the induction or challenge phases of this maximization study. It was concluded that 0.018% active CAPB in a facial cleanser was not likely to cause contact sensitivity reactions under normal use conditions.

Almondamidopropyl betaine and olivamidopropyl betaine. The irritation/sensitization potential of 0.005% almondamidopropyl betaine and 0.005% olivamidopropyl betaine in a body cleanser (a 0.5% dilution of 1% active almondamidopropyl betaine and 1% active olivamidopropyl betaine) was evaluated in a repeat insult patch test of 103 participants. [Estimated dose/unit area for each betaine = 2.5 $\mu g/cm^2$]. After the induction phase (3× per week for 3 weeks) and a 2-week rest period, the participants received a single challenge patch. No reactions were observed. It was concluded that a body cleanser containing 0.005% almondamidopropyl betaine and 0.005% olivamidopropyl betaine was not a primary sensitizer or irritant to the skin.[64]

Capryl/capramidopropyl betaine. KGL, Inc evaluated the contact-sensitizing potential of a mousse (concentrate) containing 1.72% active capryl/capramidopropyl betaine in a maximization study.[65] Twenty-six adult participants completed the study. During the induction phase, ~0.05 mL of aqueous SLS (0.25%) was applied to a test sites on the upper outer arm, volar forearm, or the back of each participant. After 24 hours, the SLS patch was removed and 0.05 mL of the test material was applied to the same site and occluded. [Estimated dose/unit area = 4.9×10^2 $\mu g/cm^2$]. The induction patch was left in place for 48 hours (72 hours if placed over a weekend). After patch removal, the site was examined for irritation. If no irritation was observed, the sequence of patching with SLS followed by patching with the test material was repeated for a total of 5 induction exposures. If irritation was observed during the induction phase, the SLS patch step was eliminated for that participant and only the test material was applied.

At the end of the induction period and a 10-day rest period, a single challenge application of 0.05 mL of the test material was made to a new skin site pretreated with ~0.05 mL of 5% SLS under occlusion for 1 hour. After 48 hours, the patch was removed and graded on a scale of 0 (*not sensitized*) to 3 (*strong sensitization*; large vesiculo-bullous reaction) 1 hour and 24 hours after removal. No adverse or unexpected reactions occurred, and no incidences of contact allergy were recorded. The study concluded that the mousse (concentrate) containing 1.72% capryl/capramidopropyl betaine did not have a detectable contact-sensitizing potential and was not likely to cause contact sensitivity reactions under normal use conditions.[65]

Lauramidopropyl betaine. Consumer Product Testing Company performed a repeated insult patch test on a shampoo with 0.042% lauramidopropyl betaine (test material was prepared as a 1% dilution in distilled water of 4.2% active lauramidopropyl betaine).[67] [Estimated dose/unit area = 2.3×10^1 $\mu g/cm^2$]. Fifty-one participants completed the study. A total of 9 applications were made during the induction phase. Following a 2-week rest period, a challenge patch was applied to a virgin test site on the back. After 24 hours, the patch was removed and the site was scored 24 and 72 hours postapplication. No reactions were observed in any of the participants during the induction or challenge phases of this study. The study concluded that the shampoo containing 4.2% lauramidopropyl betaine, diluted to 1%, did not indicate a potential or dermal irritation or allergic contact sensitization.

In another human repeated insult patch test, the potential of a body cleanser with 0.03955% lauramidopropyl betaine (a 1% dilution of 3.955% active lauramidopropyl betaine) to cause dermal irritation and sensitization was studied.[68] One hundred and nine participants completed the study. Prior to patch application, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test solution was applied to the upper back and remained in direct skin contact for 24 hours. The induction period was comprised of a total of 9 applications on the same site. The sites were graded for dermal irritation 24 hours after patch removal. Following a 2-week rest period, a challenge patch was applied to a virgin test site on the back. After 24 hours, the patch was removed and evaluated for dermal reactions. The sites were reevaluated at 48 and 72 hours. Several participants had barely perceptible erythema and reactions were observed on 1 or 2 days of induction phase of the study. No incidences of dermal reaction were recorded during the challenge phase. The study concluded that the body cleanser with 3.955% lauramidopropyl betaine, diluted to 1%, did not demonstrate a potential for eliciting dermal irritation or sensitization.

A maximization study to evaluate the contact-sensitizing potential of a shower gel containing 14% active lauramidopropyl betaine was conducted by KGL, Inc.[66] The shower gel was tested as received, namely, 0.5% aqueous. Twenty-five adult volunteers completed the study. The study was conducted in the same manner as the capryl/capramdiopropyl betaine maximization study described above, with the exception that

~0.1 mL of aqueous SLS (0.25%) and 0.1 mL of the test material were used during the induction and challenge phases. [Estimated dose/unit area = 2.8×10^2 μg/cm^2]. No adverse or unexpected reactions occurred, and no incidences of contact allergy were recorded. The study concluded that the shower gel containing 14% lauramidopropyl betaine did not have a detectable contact-sensitizing potential and was not likely to cause contact sensitivity reactions under normal use conditions.

Shea butteramidopropyl betaine. In a human repeated insult patch test, the potential of a body scrub containing 0.04% shea butteramidopropyl betaine (a 1% w/v dilution of 4.0% active shea butteramidopropyl betaine) to cause dermal irritation and sensitization was studied.[70] One hundred and one participants completed the study. The study followed standard RIPT methodology with a total of 9 induction applications of 24 hours in length and a single challenge application following a 2-week rest period. No adverse events were reported and no incidences of dermal reaction were recorded during the challenge phase. The study concluded that the body scrub with 4.0% shea butteramidopropyl betaine, diluted to 1%, was not sensitizing.

A maximization study to evaluate the contact-sensitizing potential of a body wash containing 0.0027% shea butteramidopropyl betaine (a 0.5% dilution of 0.54% active shea butteramidopropyl betaine) was conducted by KGL, Inc [Estimated dose/unit area = 7.6×10^{-1} μg/cm^2].[69] Twenty-five adult volunteers completed this RIPT study. The study was conducted in the same manner as the capryl/capramdiopropyl betaine study described above, with the exception that the patches were made only to the upper outer arm. No adverse or unexpected reactions occurred, and no incidences of contact allergy were recorded. The study concluded that the body wash containing 0.54% shea butteramidopropyl betaine did not have a detectable contact-sensitizing potential and was not likely to cause contact sensitivity reactions under normal use conditions.

Provocative Studies

In 706 patients studied for skin allergy, 93 (83 women and 10 men) were provisionally diagnosed with cosmetic contact dermatitis.[71] Four of the 93 had positive reactions to CAPB 1% aqueous. Two participants had scalp itch and erythema on the forehead, ears, and neck following the use of shampoos with CAPB. The other 2 participants had eczema on the face and/or neck following use of face cleansers that contained CAPB. From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active.

Fowler studied 210 patients clinically suspected of having allergic contact dermatitis to cosmetics and toiletries.[63] Patch testing with CAPB (1% aqueous) in addition to the North American Contact Dermatitis Group (NACDG) series (70 allergens total) was performed. Twelve of the participants (5.7%) had positive reaction to CAPB in the patch test. Positive reactions were also observed for formaldehyde or formaldehyde releasers, neomycin, and nickel. All but 2 of the participants had initially reported with head and neck dermatitis. The remaining 2 participants had hand dermatitis. Of the 12 participants, 7 were determined definitely relevant when the reported dermatitis cleared after cessation of use of products with CAPB. Specific case reports for 2 of the participants are detailed in the section on case reports. From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous.

de Groot et al studied 2 groups of patients for CAPB allergy.[59] The first group consisted of 781 patients that were patch tested with the European standard series, hairdresser's series, cosmetics series, and with other relevant allergens, including the patients' personal care products, and 1% aqueous CAPB from February 1991 to June 1994. Most of the patients in this group were suspected of having occupational contact dermatitis (217 patients were hairdressers). The second group was studied in approximately the same time period and consisted of 102 patients suspected of having cosmetic dermatitis. The patients were patch tested with 1% aqueous CAPB along with the cosmetic screening series. In both groups, relevance was only declared if the patients used products with CAPB and if their dermatitis cleared upon cessation of use of these products.

In the first test group, 56 patients (7.2%) had positive reactions to CAPB, and of these, 17 were classified as definite and all used shampoos and/or shower gels that contained CAPB. Eight of the 17 were hairdressers and had experienced dermatitis on their hands. In the second test group, only 3 patients (3%) had a positive reaction to CAPB. The patients had been using shower gels, shampoos, and/or body lotions containing CAPB. From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous.

Armstrong et al patch tested patients with suspected contact dermatitis (from January 1991 to September 1998) with a standard series that included 1% aqueous tegobetaine L7 (from 1991 to 1994) or 1% aqueous CAPB (from 1995 to 1998). The authors noted that the latter had significantly lower intermediate and reactant impurities.[60] Of the 10 798 patients tested, 29 (0.27%) had a positive reaction to CAPB (24 reactions to tegobetaine L7). Twenty-three of the 29 cases were deemed relevant and had reported dermatitis on the face, neck, hands, or widespread areas. The authors suggested that higher purity CAPB was linked to a diminished frequency of CAPB sensitization. From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous.

In a double-blind randomized controlled study to evaluate allergenicity to coconut oil derivatives, 10 control participants and 12 participants with previously diagnosed allergy to CAPB were patch tested with 11 coconut-derived surfactants, coconut oil, and lauric acid.[61] Patch testing was performed in random order according to standardized procedures with readings at 48 and 96 hours. Three of the 12 participants had doubtful reactions to CAPB in the patch test and 1 control participant had a doubtful reaction to CAPB. The authors suggested that

Table 8. Eye Irritation Studies on CAPB

Concentration	No./strain of rabbit	Results	Reference
4.5% active[b]	6/albino	Slight conjunctival irritation in 3 unrinsed eyes. Very slight conjunctival irritation in 2 of 3 rinsed eyes.	86
30% active[b]	3/albino	Diffuse corneal opacity at day 3. Mild conjunctival erythema, chemosis, and discharge from day 1. Slight iritis on day 4.	87
6% active solution	3/albino	Mild conjunctival erythema and slight discharge, cleared by day 3.	88
7.5% active, pH 8.3	6/NZW	Mild to moderate conjunctival irritation after 24 h, disappearing by day 6.	89
10% active[b], pH 6.1	1/albino	Max. unrinsed score = 30 after day 3, 7 by day 7.	47
30% active[a]	9/NZW	Max. mean score (unrinsed, n = 6) = 41.7 after 72 h, decreased to 27.2 after 7 days (scale 0 - 110). Minimal irritation in rinsed eyes (n = 3).	90
8.6% active[a]	9/NZW	Max unrinsed score = 25.7 after 24 h, 0 by day 7. Mean score rinsed (n = 3) = 2.0 after 24 h, 0 by 48 h.	91
5%	6/NZW	Draize score = 4.90. Not an ocular irritant.	92
10%	6/NZW	Draize score = 27.3. Moderately irritating.	93
3.0% active	6/albino	Corneal irritation day 3 - 7. Iritis and conjunctival irritation lessens in severity by day 7.	94
3.0% active	6/albino	No corneal irritation. Iritis and conjunctival irritation clear by day 7.	94
3.0% active	6/albino	Average ocular index = 41.6/110. Ocular irritant.	95,96
Soap formulation containing 2.3% active[b] CAPB	9/NZW	Max mean score (unrinsed, n = 6) = 18.7, primarily irritation of iris and conjunctiva. Max mean score (rinsed, n = 3) = 20.0.	97
Soap formulation containing 2.3% active[b] CAPB	9/NZW	Max mean score (unrinsed, n = 6) = 1.7. Max mean score (rinsed, n = 3) = 3.3. Primarily conjunctival irritation.	98
Soap formulation containing 6.5% active[b] CAPB	4/NZW	Max total score = 30.0 (max 110). Irritation of cornea, iris, and conjunctiva. Moderately irritating.	99
Formulation containing 6.0% active[b] CAPB	6/albino	Conjunctival irritation after day 1.	1

[a] Reference cited as % solids.
[b] Referenced as full strength.

doubtful reactions to CAPB represent irritant reactions and not allergic reactions.

Photosensitization

An investigation of the potential of a 3.0% active aqueous solution of CAPB to induce contact photoallergy was tested using 30 human participants. The 11 participants who had mild to moderate erythemic responses at the irradiated sites during the induction testing were those that received both UVA and 2 MED of UVB irradiation (source spectrum not reported). These responses were expected from the UVB exposure alone. The CAPB was not a photosensitizer in this study.[55]

Case Reports

Numerous case studies of allergic contact dermatitis reported positive patch tests to CAPB at concentration as low as 0.5%.[72-84]

Ocular Irritation

The available data on ocular irritation studies are summarized in Table 8. Two groups of 3 albino rabbits received 0.1 mL instillations of 4.5% active solution of CAPB into the conjunctival sac of 1 eye.[85] Treated eyes of one group were rinsed, but the treated eyes of the other group were not rinsed. Slight conjunctival erythema and chemosis were noted in all treated, unrinsed eyes by day 2 following instillation and subsided by day 7. Slight conjunctival irritation was observed in 2 of the 3 treated, rinsed eyes on the first 2 days of observation. There was no corneal involvement or iris congestion.

The CAPB (30% active) was instilled (0.1 mL) into the conjunctival sac of 1 of the eyes of 3 albino rabbits using the Draize method.[87] Diffuse corneal opacity was observed by day 3 following instillation. Slight iritis was observed by day 4. Mild conjunctival erythema, chemosis, and discharge were noted from day 1.

Three albino rabbits received a 0.1 mL instillation of a 6% active CAPB solution into the conjunctival sac of the right eye.[88] Mild conjunctival erythema and slight discharge were observed in all treated eyes for the first 2 days after instillation, clearing by the third day.

Six NZW rabbits (body weight range 2.4-2.6 kg) received an instillation of 0.1 mL of 7.5% active CAPB with a pH of 8.3 into the conjunctival sac of the left eye.[89] Mild to moderate conjunctival irritation was observed in all treated eyes after 24 hours. The treated eye of 1 rabbit had moderate corneal opacity after the second day. These alterations disappeared by the sixth day after instillation.

One rabbit receiving a 0.1 mL administration of a 10% active CAPB solution (pH 6.1) had Draize scores of 28 after day 1, 25 after day 2, 30 after day 3, 14 after day 4, and 7 after day 7 of the observation period.[47]

A full-strength sample of CAPB (30% active) was tested for ocular irritation using 9 NZW rabbits.[90] A volume of 0.1 mL was instilled into the conjunctival sac of one eye of each rabbit. Mean eye irritation scores for treated, unrinsed eyes were 32.5 ± 4.4 after 24 hours, 31.7 ± 3.3 after 48 hours, 41.7 ± 11.7 after 72 hours, and 27.2 ± 11.4 after 7 days (scale 0-110). Corneal opacity, slight iritis, and conjunctival irritation and necrosis were noted in treated, unrinsed eyes. Under these conditions, the sample was considered corrosive. Minimal irritation (mean score = 10.0 ± 2.0 after 24 hours), subsiding after 48 hours, was noted in treated eyes that had been rinsed.

An instillation of 0.1 mL of a sample of 10% active CAPB was made into the conjunctival sac of 1 of the eyes of 9 NZW rabbits.[91] Mean eye irritation scores for treated, unrinsed eyes were 25.7 ± 8.3 after 24 hours, 16.7 ± 10.9 after 48 hours, and 9.3 ± 11.4 after 72 hours. No irritation was observed on day 7. Treated, rinsed eyes had a mean score of 2.0 ± 2.0 after 24 hours, returning to normal after 48 hours. The CAPB sample was considered moderately irritating to treated, unrinsed eyes and practically nonirritating to treated, rinsed eyes under these conditions.

In 2 ocular irritation studies by Hazelton Laboratories, 0.1 mL of either 5% or 10% CAPB was instilled into the left eye of groups of 6 NZW rabbits.[92,93] The CAPB was not an ocular irritant in the 5% group (Draize score = 4.90) but was considered moderately irritating in the 10% group (Draize score = 27.3).

In a Draize test for ocular irritation, two 3.0% active CAPB samples were instilled into the conjunctival sac of 6 albino rabbits.[94] Scores for corneal irritation were 0 for the first 2 observation days, 1.66 for the third and fourth days, and 4.16 on the seventh day (max score = 80) for 1 of the CAPB samples. No corneal irritation was observed in eyes treated with the other sample. Both samples produced iritis by the first day (scores of 8.33 and 5, respectively, on a scale of 0-10), which decreased in severity by the seventh day (scores of 4.16 and 0, respectively). Both samples produced conjunctival irritation (scores of 15.37 and 14.33, respectively, on a scale of 0-20), which decreased in severity by the seventh day (scores of 6 and 0, respectively).

A 3.0% active CAPB sample was tested for ocular irritation using 6 male albino rabbits.[95,96] The average ocular index was 41.6 (max = 110) 24 hours after instillation of 0.1 mL of the sample. The sample was considered an ocular irritant.

A volume of 0.1 mL of a liquid soap formulation containing 2.3% active CAPB was instilled into the conjunctival sac of each of 9 NZW rabbits.[97] An average irritation score of 18.7 (max 110) was calculated for unrinsed eyes, which compared with 20.0 for rinsed eyes. Irritation was observed primarily in the iris and conjunctiva. Under both sets of conditions, the liquid soap formulation was considered moderately irritating.

Another liquid formulation containing 2.3% active CAPB was tested for ocular irritation using 9 NZW rabbits.[98] The maximum average irritation score for the 6 treated, unrinsed eyes was 1.7 (max 110). Slight conjunctival erythema and chemosis were observed in 1 rabbit 2 days after treatment and in the eye of another for the entire 7-day observation period. Slight discharge also was observed in the treated eye of the latter from 72 hours to 7 days following treatment. The formulation was considered minimally irritating to treated, unrinsed eyes of rabbits. The maximum average irritation score for the 3 treated, rinsed eyes was 3.3. Mild conjunctival erythema and chemosis were observed in all tested eyes 1 to 2 days following the instillation. The formulation was considered mildly irritating to treated, rinsed eyes of rabbits.

A liquid soap formulation containing 6.5% active CAPB was tested for ocular irritation by instilling 0.1 mL into the conjunctival sac of one eye of each of 4 NZW rabbits, followed by rinsing.[99] Mean corneal irritation scores were 13.8 after 1 hour, 18.8 after 24 hours, 11.3 after 48 hours, 5 after 72 hours, and 1.3 after 7 days (max 80). Mean iridial irritation scores were 3.8 after 1 hour and 24 hours, decreasing to 0 after 7 days. Mean conjunctival irritation scores were 11 after 1 hour, 7.5 after 24 hours, 4 after 48 hours, 3.5 after 72 hours, and 2 after 7 days. No irritation was observed 14 days after the instillation. With a total mean irritation score of 30.0 (max. total = 110.0), the formulation was considered moderately irritating.

A single 0.1 mL dose of a product formulation containing 6.0% active CAPB was instilled into the conjunctival sac of each of 6 albino rabbits in a Draize test.[1] Conjunctival irritation (mean score of 4; max = 20) was observed in all treated eyes on the first day following instillation, decreasing in severity on the second day. No corneal irritation or iritis was observed.

Mucous Membrane Irritation

Two soap formulations containing 7.5% CAPB were tested for vaginal irritation potential in Beagle dogs (7-10 months old; 8.2-10 kg). The formulations were tested in 3 dogs each. Prior to treatment and again before termination, hematology, clinical chemistry, and urinalysis were performed. A volume of 20 mL of the test material was administered into the vagina via a syringe once a day for 15 days (weekdays only). Vaginas and vulvas were examined 6 hours prior to and after each daily treatment. At termination of the study, the dogs were killed and necropsied. Tissue samples of the liver, kidney, and vulva/vagina were examined. Blood was found in the urine of 5/6 dogs. Gross necropsy revealed discoloration of the lining of the vagina in 5/6 dogs. Diffuse necrosis of vaginal mucosa occurred in 5/6 dogs and focal vaginal necrosis occurred in 1 dog (this dog was in estrus). There was corresponding inflammatory cell infiltration (mainly neutrophils) and often a fibrinopurulent membrane adherent to the injured surface. It was concluded that lesions were the result of test material application. Morphologic changes in the liver and kidneys in all dogs were not considered significant and were within normal parameters.[100,101] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 7.5% active or 7.5% aqueous, which equated to 2.25% active.)

Genotoxicity

Bacterial Assays

A commercial sample of CAPB (31.0% active) was tested using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, both with and without metabolic activation. The concentrations of CAPB solution tested were 0.004, 0.02, 0.1, 0.2, and 0.4 μL/plate. The CAPB is toxic above 0.3 μL/plate. The test material did not cause a significant increase in mutation frequency in any of the strains tested with or without metabolic activation.[102]

CAPB (30% active) was tested using *S typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, with and without metabolic activation. Eight concentrations between 0.001 and 0.300 μL/plate were used, based on CAPB solubility. The CAPB did not produce an increase in mutation frequency, with or without metabolic activation.[103]

In a study summarized by the American Chemistry Council, CAPB (28.5-30.5% active) was tested using *S typhimurium* strains TA98, TA1535, TA1537, and TA1538, both with and without metabolic activation at 0, 50, 150, 500, 1500, or 5000 μg/plate.[35] Positive controls were *N*-ethyl-N'-nitro-*N*-nitroso-guanidine (for TA100 and TA1535), 9-aminoacridine (for TA1537), 4-nitro-o-phenylenediamine (for TA1538), 4-nitroquinoline-1-oxide (for TA98), and 2-aminoanthracene (in all strains with metabolic activation only). Cytotoxicity was observed at 150 μL/plate and above. The CAPB in this assay was found to be nonmutagenic.

The American Chemistry Council also summarized the findings of a CAPB (concentration not stated) mutagenicity assay using *S typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, with and without metabolic activation.[35] The test material was tested at 1, 4, 16, 64, or 256 μg/plate without S-9 activation and at 4, 16, 64, 256, and 1024 μg/plate with S-9 activation. The CAPB did not increase the mutation frequency, with or without metabolic activation.

Mammalian Cell Assays

The mutagenic potential of a 30.9% active sample of CAPB was tested in a L5178Y TK ± mouse lymphoma assay with and without metabolic activation. The test substance was solubilized in water and diluted for testing at concentrations of 0.001, 0.01, 0.1, 1.0, 10, and 100 μL/mL. None of the treated cultures had a significant increase in mutation frequency over the average mutant frequency of the solvent controls.[104]

Animal Assays

The American Chemistry Council summarized a mouse micronucleus test that studied CAPB (concentration not stated).[35] Groups of 5 male and 5 female OF1 mice received 2 doses of either 0.02 or 0.2 g/kg of the test material in sterile distilled water via intraperitoneal injection (dose volume 10 g/kg) at 24-hour intervals. Negative and positive controls received sterile distilled water and cyclophosphamide, respectively. The rats were killed 6 hours after the second administration of the test material and bone marrow slides were prepared. One thousand polychromatic erythrocytes (PCEs) per animal were studied for the presence of micronuclei. In both dose groups, the number of micronucleated PCEs was not increased when compared to the negative control. The positive control group yielded expected results. The CAPB was not a mutagen under the conditions of this study.

Carcinogenicity

An aqueous preparation of a nonoxidative hair dye formulation containing an unspecified grade of CAPB at a concentration of 0.09% active CAPB was tested for carcinogenicity using groups of 60 male and female random-bred Swiss Webster mice from the Eppley colony.[105] The formulation also contained 5% propylene glycol, 4% benzyl alcohol, 0.6% kelzan (xanthan gum), 0.9% lactic acid, 0.04% fragrance, and less than 0.1% each of the disperse brown, red, yellow, and blue dyes. 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 and shaved. Mortality, behavior, and physical appearance of the mice were observed daily. Dermal changes in particular were noted. Body weights were recorded weekly. Ten males and 10 females from each group were killed at 9 months for a hematological study, urinalysis, and necropsy. At termination, all mice were necropsied, and the tissues were examined microscopically. No adverse effects were noted on average body weight gains, survival, hematological or urinalysis values in any group. Varying degrees of chronic inflammation of the skin were seen in all groups, including controls. Other lesions occurred but were considered unrelated to hair dye treatment. The incidence of neoplasms in treated animals did not differ significantly from control groups.

Irritation/Sensitization Studies With Amidoamine, DMAPA, and Related Amines

Amidoamine is a term used for fatty acid esters of amidopropyl dimethylamine, intermediates in the synthesis of the amidopropyl betaines; DMAPA is also an intermediate in the synthesis of the amidopropyl betaines. These compounds can exist as impurities in cosmetic formulations containing amidopropyl betaines.

Animal Studies

Hill Top Research, Inc performed a delayed contact hypersensitivity study of stearamidopropyl dimethylamine in guinea pigs.[106] A pre-induction primary irritation study was conducted to determine the concentration for the induction phase of the study. Twenty Hartley outbred guinea pigs were treated with 1.0% w/v stearamidopropyl dimethylamine in 80% ethanol/20% distilled water. The test material was applied for 6 hours at a dose volume of 0.3 mL using 25 mm diameter occluded Hill Top chambers on clipped, intact skin on the left shoulder.

[Estimated dose/unit area = 6.1×10^2 μg/cm^2]. The exposure sites were rinsed after removal of chambers and re-exposed once a week for a total of 3 exposures. A control group of 10 guinea pigs received the vehicle alone. After a 2-week rest period, the animals received primary challenge patches of 0.25% w/v stearamidopropyl dimethylamine in acetone on naive skin. [Estimated dose/unit area = 1.5×10^2 μg/cm^2]. One guinea pig had delayed contact hypersensitivity to the test material. The control animals had no reactions. A rechallenge was conducted in 6 guinea pigs 13 days after the primary challenge with 0.25%, 0.125%, and 0.0625% w/v stearamidopropyl dimethylamine. An additional 5 animals were used as controls. One guinea pig had a positive response to the test material at 0.25%. No other reactions were observed.

Palmityl/stearylamidopropyl dimethylamine at a concentration of 25% active in 8.95% phosphoric acid and 66.05% water was studied for delayed contact hypersensitivity using albino Dunkin/Hartley guinea pigs.[107] A preliminary irritation test was conducted to determine the maximum concentration for the induction and challenge phases of the study. In the induction phase, 10 male and 10 female animals received 0.4 mL of test material on a 4 cm^2 patch on the clipped skin of the left shoulder for a period of 6 hours. [Estimated dose/unit area = 2.5×10^4 μg/cm^2]. The patches were occluded. An additional 5 male and 5 female animals were left untreated as the controls. A total of 3 induction patches were applied, once weekly, for 3 weeks. Following a 2-week rest period, all animals received primary challenge patches of 0.4 mL of test material on the right flank for 6 hours. The test sites were scored at 24 and 48 hours postapplication. All but 3 of the 20 guinea pigs had patchy to severe erythema at the 24- and 48-hour observation periods. Four control animals had slight to moderate patchy erythema during the observation periods. Rechallenges were conducted on 0.25% active and 0.5% active palmityl/stearylamidopropyl dimethylamine. No sensitization was observed with the 0.25% active material, but 0.5% active material elicited reactions in sensitized animals. The study concluded that palmityl/stearylamidopropyl dimethylamine had the potential to cause delayed contact hypersensitivity in guinea pigs.

Two guinea pig maximization studies to assess the skin sensitization potential of amidoamine were evaluated.[71] In the first study, preliminary tests determined the maximum concentrations of intradermal injections, topical induction, and challenge applications. Ten albino Dunkin/Hartley guinea pigs (6 females and 4 males) received two 0.1 mL injections of 50% Freund complete adjuvant at the first pair of sites, two 0.1 mL injections of 0.1% amidoamine at the second pair of sites, and two 0.1 mL injections of amidoamine in DOBS/saline vehicle and Freund complete adjuvant (50/50 ratio) to yield a final concentration of 0.1% amidoamine at the third pair of sites. One week following the injections, a single occlusive 48-hour induction patch (2 × 4 cm) of 0.2 to 0.3 mL amidoamine 5% in acetone/PEG400 vehicle was applied to the same shaved area. Four male control animals received intradermal injections and induction patches using only the vehicles. Two weeks after the induction patch, all animals received a single occlusive 24-hour challenge patch (8 mm diameter patch in a Finn chamber) saturated with 0.5% amidoamine in acetone/PEG 400 on a clipped and shaved flank. The treatment sites were examined 24 and 48 hours after patch removal. Two more challenges were made 1 and 2 weeks after the first challenge. Reactions were scored on a scale of 0 (*no reaction*) to 3 (*severe erythema and edema*).

At the first challenge, 7 animals had a reaction score of $\geq$0.5 at 24 hours after the removal of the patch. After 48 hours, 6 animals had a reaction $\geq$0.5. Three out of 10 animals had a reaction score of 2. At the second challenge, 7 guinea pigs had a score of $\geq$0.5 at 24 hours after patch removal. These scores were consistent at the 48-hour reading. Five out of 10 animals had a reaction score of 2. At the third challenge, all 10 guinea pigs had a score $\geq$1 at 24 hours after patch removal. These score remained largely consistent at the 48-hour reading. Eight of the 10 animals had a reaction score of 2. The study concluded that amidoamine was a moderate sensitizer.[71]

The second maximization study was conducted in the same manner as the first with the only changes being that 0.025% amidoamine was used in the intradermal injections instead of 0.1%, 1% amidoamine was used in the topical induction, only 2 challenges were made, and 4 female guinea pigs were used as controls.

At the first challenge, 3 animals had a reaction score of $\geq$1 at both the 24- and 48-hour readings, with 1 of the animals scoring a 2. At the second challenge, 3 animals had a reaction score of $\geq$1 at 24- and 48-hour readings, although 1 animal had no reaction at 48 hours had 1 at 24 hours, while another that had no reaction at 24 hours had 1 at 48 hours. The study concluded that amidoamine was a moderate sensitizer.[71]

Wright et al reported on the results of an LLNA study performed on 4 chemicals that are recognized human contact allergens, including DMAPA (99.0+ % pure).[72] The chemicals were tested in 7 different vehicles: acetone, olive oil (4:1), dimethylsulfoxide, methethylketone, dimethyl formamide, propylene glycol, and 50:50 and 90:10 mixtures of ethanol and water. Groups of 4 female CBA/Ca mice were exposed topically on the dorsum of both ears to 25 μL of 0.5%, 1.0%, 2.5%, 5.0%, or 10.0% of the test material, or to an equal volume of the appropriate vehicle alone, daily for 3 consecutive days. Five days after the initial topical treatment, all animals were injected intravenously with 20 μCi of [^{3}H] methyl thymidine. Approximately 5 hours after injection, the animals were killed and the auricular lymph nodes were excised. Single-cell suspensions were prepared from pooled lymph nodes, with the cells precipitated by trichloroacetic acid (TCA), and the radioactivity measured by liquid scintillation. The stimulation indices (SIs) were calculated, and at 10.0% DMAPA ranged from 2.2 in propylene glycol to 15.7 in dimethyl formamide. The estimated concentrations for a SI of 3 (EC_3) ranged from 1.7% (in dimethyl formamide) to >10% (in propylene glycol).

An LLNA study was performed using stearamidopropyl dimethylamine (TEGO AMID S 18).[108] A certificate of analysis reported that the DMAPA level conformed to the $\leq$20 ppm limit, the amine value was 150.8 mg KOH/g (limit

range = 148.0-152.0 mg KOH/g), and the melting point was 68.0°C (limit range 66.0°C-69.0°C).[109] CBA/Ca female mice were divided into 5 groups of 4 and received 0.1%, 0.5%, 1%, 2.5%, or 5% (w/v) of the test material in ethanol/water (7/3, v/v) on the dorsum of each ear lobe (25 µL per ear, diameter ~8 mm) once daily for 3 consecutive days. A control group of 4 mice was treated with the vehicle only. The positive control group received α-hexylcinnamaldehyde in acetone:olive oil (4:1, v/v). The mice were treated with [^{3}H] methyl thymidine, killed, and the lymph nodes were prepared in the manner as described in the previous study.

No deaths occurred during the treatment period in any dose group. No clinical signs of toxicity were observed during treatment in the control group or in the 0.1% and 0.5% dose groups. Slight to moderate ear erythema was observed after the second or third application at both dosing sites in all mice in the 1%, 2.5%, and the 5% dose groups. This persisted for 2 days in the 1% dose group and until treatment end in the 2.5% and 5% dose groups. Body weight development was not affected in any of the animals. The SIs were1.4, 2.1, 2.1, 5.8, and 3.9 for the 0.1%, 0.5%, 1%, 2.5%, and 5% dose groups, respectively. The EC_3 was calculated at 1.4%. The positive control group had expected results and validated the study. The study concluded that steramidopropyl dimethylamine (TEGO AMID S 18) was a potential skin sensitizer in this LLNA test.[108]

Calvert Laboratories, Inc performed an LLNA study using amidoamine (~99% C12-C18).[110] A preliminary dose range study was performed. In the main study, groups of 5 mice received 0%, 0.1%, 0.5%, 1%, 2.5%, or 5% of the test material in ethanol/water, 7:3 (v/v) neutralized to pH 6.0 with citric acid monohydrate. An additional 5 mice received the positive control, 35% hexylcinnamaldehyde. The mice were treated on the dorsal surface of both ears (25 µL/ear) once daily for 3 days. On day 6, the mice were injected intravenously (iv) with 20 µCi of ^{3}H-thymidine. Five hours later, the mice were killed and the draining auricular lymph nodes were removed, processed, and assessed for lymphocyte proliferation. No mortality or adverse effects were observed throughout the study. Very slight erythema was observed on day 3 and very slight erythema and edema were observed on days 4 to 6 of the 2.5% dose group. In the 5% dose group, 4 of the 5 mice treated had very slight erythema and very slight edema on day 2. On days 3 to 6, mice in this dose group had well-defined erythema and slight edema. The SIs were 1.8, 1.0, 3.1, 24.5, and 60.6 for the 0.1%, 0.5%, 1%, 2.5%, or 5% dose groups, respectively. The EC_3 for amidoamine was calculated at 0.98%. The positive control group had expected results and validated the study. This LLNA study concluded that amidoamine has skin-sensitizing activity.

Human Studies

Hill Top Research, Inc performed an investigation of the potential of stearamidopropyl dimethylamine to induce skin sensitization in 112 human participants. [73] Applications contained a concentration of 0.25% w/v of the test material in undiluted mineral oil. Induction applications of 0.3 mL were made to the same site, with a Webril patch for a total of 9 applications. Challenge applications were made to naive alternate sites. Frequent incidences of slight to moderate irritation, including erythema, some edema, papules, glazing, and cracking, were observed during the induction period but were considered transient. Five participants had a reaction of grade 1 or greater during the challenge phase. The responses to stearamidopropyl dimethylamine were indicative of primary irritation rather than contact sensitization.

In a study by Inveresk Research International, the sensitization potential of a 4% aqueous liquid fabric softener formulation containing 0.5% stearyl/palmitylamidopropyl dimethylamine was investigated using 77 participants.[74] During the induction phase, the test material was applied at a dose volume of 0.5 mL with a ¾ inch square Webril pad to the dorsal surface of the upper arm. [Estimated dose/unit area = 6.9×10^2 µg/cm^2]. Patches were applied for a duration of 24 hours, 9 times over a period of 3 weeks. The test material caused some degree of irritation in most volunteers. After a rest period of 2 weeks, the participants received challenge patches with the same concentration of test material on both arms. Patch sites were graded 48 and 96 hours after patching. Eight participants reacted at challenge, and 7 submitted to rechallenge with 4% and 0.4% aqueous formulations. No reactions indicative of sensitization occurred at rechallenge. The test formulation containing stearyl/palmitylamidopropyl dimethylamine had no significant sensitization potential.

Foti et al patch tested 285 consecutive dermatitis patients with the European standard series supplemented with oleamidopropyl dimethylamine (0.5% aqueous), CAPB (1% aqueous), and DMAPA (1% aqueous).[75] The standard patching technique was employed and test sites were scored on days 2, 3, 4, and 7. Twenty-three patients (8%) had allergic responses to DMAPA, 14 patients (4.9%) had allergic responses to DMAPA and oleamidopropyl dimethylamine, and 8 patients (2.8%) had allergic responses to all 3 of the supplemental chemicals. Analyses by thin-layer chromatography (TLC) of the oleamidopropyl dimethyl amine sample revealed contamination by DMAPA (6 ppm or 0.12% of the sample) and indicated that the allergic responses in the last group were not due to cross-reaction. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

In a 2-year study by Pigatto et al, 1190 patients with eczema were patch tested with 1% aqueous CAPB using standard technique and grading according to the European Contact Dermatitis Group (ECDG).[76] From this patch test, 17 patients were diagnosed with allergic contact dermatitis to CAPB. Relevance was established with an additional positive patch test of 2+ or more to at least 1 personal care product containing CAPB used by the patients. Fifteen patients were further tested with CAPB 0.01%, 0.5%, 1% (from 2 different manufactures), and 2% in water; and DMAPA at 0.05%, 0.1%, and 1% in petrolatum; and, if possible, the patients' reported cosmetics diluted in water at 1:10, 1:100, and 1:1000.

In 12 patients tested with their own personal cosmetics, 9 had positive reactions to at least 1 dilution and 5 had irritant reactions. All except 3 patients, who were not tested, had 2 or 3+ reaction to DMAPA at concentrations as low as 0.05%. Only 1 patient had a positive reaction to CAPB. The presence of DMAPA was investigated via TLC in the personal cosmetics of 4 of the patients that had positive reactions. These positive reactions from DMAPA suggest that the positive reaction to CAPB-containing products was likely due to a certain concentration of DMAPA that was an impurity. The DMAPA was measured in the products at 50 to 150 ppm. The concentration of DMAPA was also measured in the 2 CAPB types: one had a concentration of DMAPA at 200 ppm and DMAPA was below detection level (level not reported) in the other type. The authors stated that the sensitizing agent in CAPB allergy is DMAPA, although their findings did not exclude the role of CAPB itself from causing allergic dermatitis.[76] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

A study of sensitization to commercially available CAPB in patients with dermatitis was performed by Angelini et al.[77] Twelve hundred consecutive patients with dermatitis of various types were patch tested with the European standard series and CAPB 1% aqueous (30% active ingredient). Some of the patients that had allergic or irritant reactions to CAPB were then patch tested with the chemicals that were intermediates or reactants in the synthesis of CAPB (amidoamine, DMAPA, and monochloroacetic acid) along with a sample of CAPB of greater purity and Tego 103 G 1% aqueous.

Positive allergic reactions to CAPB were observed in 46 participants (3.8%), while irritant reactions were recorded in 15 participants (1.25%). Of these 46 participants, 30 had positive reactions to DMAPA 1% aqueous. In these 30 participants, 3 and 16 were positive to the purer grade of CAPB 0.5% aqueous and CAPB 1% aqueous, respectively. Patients with irritant reactions had negative reactions to the synthetic materials and to the purer grade of CAPB. No allergic or irritant reactions to DMAPA were observed in 50 healthy controls. No positive reactions to amidoamine 0.05% were observed. The authors concluded that the results suggested that DMAPA impurity was responsible for CAPB allergy.[77] (From the study documentation, it was not possible to determine whether the administered CAPB concentrations were 0.5% active and 1% active or 0.5% aqueous and 1% aqueous, which equated to 0.15% active and 0.3% active, respectively.)

A further study by Angelini et al was performed to determine whether CAPB or an impurity of CAPB was responsible for cases of contact dermatitis.[78] In this study, TLC was employed to analyze a sample of CAPB (Tego Betaine F 30% solution) and isolate and identify unknown impurities other than DMAPA, chloroacetic acid, and amidoamine found in the CAPB solution. An infrared spectrum analysis was used to confirm the presence of the sodium salt of *N,N*-dimethyl-propylene-diaminotriacetic acid.

Upon identifying the impurity, 30 patients with a history of contact allergy to 1% aqueous CAPB and 1% DMAPA were patch tested with pure CAPB and a blend containing sodium chloride and *N,N*-dimethyl-propylene-diaminotriacetic acid (both at 1%). None of the participants reacted to any of the chemicals. The authors suggested that pure CAPB, chloroacetic acid, amidoamine, and *N,N*-dimethyl-propylene-diaminotriacetic acid were not the components responsible for CAPB sensitivity and the involvement of DMAPA cannot be ruled out.[78] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

In another study by Angelini et al, DMAPA was tested at varying concentrations with other tensioactive chemicals to determine whether they enhanced sensitivity to DMAPA.[79] Thirty-four participants with confirmed contact allergy to 1% aqueous DMAPA were patch tested with DMAPA in water, DMAPA in a SLES 2% aqueous solution, and DMAPA in a polysorbate 20 2% aqueous solution, all in decreasing concentrations from 0.1% to 0.00005%. The participants were also patch tested with CAPB and a series of 10 substances chemically related to DMAPA. Test sites were occluded for 2 days and the sites were measured for reactions on days 2, 3, 4, and 7.

Eighteen participants had positive reaction to DMAPA in water at 0.1%. No positive reactions were noted for DMAPA in water at 0.01% to 0.00005%. Positive reactions were observed in DMAPA in SLES, with 27 participants positive at the highest concentration, 10 participants positive at 0.01%, 5 participants positive at 0.005%, and 1 participant positive at 0.0001%. Positive reactions were also observed in DMAPA in polysorbate 20 in 21 participants at 0.1% and 4 participants at 0.01%. Patch tests for the chemically related structures were positive in 28 participants for *N,N*-dimethyl-2-ethylenediamine 1% aqueous, 12 participants for cocamidopropylamine oxide 1% aqueous (35% active material), and 18 participants for CAPB 1% aqueous (30% active material). No other reactions occurred. The authors concluded that tensioactives such as SLES and polysorbate 20 may enhance the risk of sensitization to DMAPA at low concentrations. They also concluded that the primary amine and the tertiary amine groups (dimethyl substituted) are the sensitizing chemical structures in DMAPA and related molecules when they are separated by 2 or 3 carbon atoms.[79]

In another study by Angelini et al, 20 patients (ages 17-51 years, 13 females and 7 males) with confirmed contact allergy to DMAPA (1% aqueous) and CAPB (1% aqueous) were tested.[80] All the patients had intolerance to detergents and shampoos and none were sensitized through an occupation. The patients were patch tested using serial dilutions of DMAPA (100 ppm) in surfactant solutions (1% or 2% w/w surfacatants) that included purified CAPB (DMAPA <1 ppm), SLES, polysorbate 20 (Tween 20), lauryl polyglucoside (APG), SLES/CAPB 3:1 (w/w), and APG/CAPB 3:2 (w/w). The test sites were scored on days 2, 3, 4, and 7. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

Positive reactions were observed in serial dilutions of DMAPA in 1% CAPB at 1 ppm and higher (1 reaction each to 1 ppm and 5 ppm DMAPA, 3 reactions to 10 ppm DMAPA, and 4 reactions to 50 ppm DMAPA). Similar positive observations were made in serial dilutions of DMAPA in 1% SLES/CAPB 3:1. No positive reactions were observed when DMAPA (100 ppm) was tested in water, but 7 positive reactions were recorded when the material was tested in 2% CAPB. A greater number of reactions were observed when 100 ppm DMAPA was mixed with 2% SLES/CAPB (5 reactions) than when mixed with 2% APG/CAPB (2 reactions). The authors noted that CAPB and SLES/CAPB 3:1 act as carriers for DMAPA when applied under occlusion at 1%, and that surface activity in more concentrated surfactant solutions may be responsible for allergic reactions by DMAPA. The authors concluded that the concentration limit for DMAPA in 1% CAPB or 1% SLES/CAPB 3:1 should be 0.5 ppm (corresponding to 15 ppm and 60 ppm, respectively) and that betaine should be blended with nonionic surfactants to reduce allergy risks.[80] (From the study documentation, it was not possible to determine whether the administered CAPB concentrations were 1% active and 2% active or 1% aqueous and 2% aqueous, which equated to 0.3% active and 0.6%, respectively.)

Uter studied 80 participants (mainly hairdressers) with dermatitis from 1996 to 1999.[81] During this period, the participants were patch tested with the hairdresser's series supplemented with DMAPA (1% pet and 1% aq Uter). The hairdresser's series contained CAPB (1% aqueous) that had a maximum residual DMAPA of <15 ppm. Of the 80 participants, 6 had + to +++ reactions to CAPB, but none of the 6 had reactions to DMAPA. A housewife with scalp and neck dermatitis had a + reaction to DMAPA 1% aqueous and a +? reaction to DMAPA 1% pet. This participant had no positive reaction to CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

McFadden et al studied 7 participants that had relevant dermatitis to CAPB.[82] The dermatitis occurred after use of liquid soaps, and in one case an eye makeup remover that contained CAPB. Four of the 7 participants were patch tested with partially purified CAPB (1% aqueous) containing <0.5% cocamidopropylamine and 0.1% and 0.01% cocamidopropylamine. The patch sites were read at day 2 and day 4 after the initial patching. One participant had a positive reaction that appeared only with cocamidopropylamine. Another had a reaction only with CAPB; however irritancy could not be ruled out since the participant's patch sites were only read on day 2. The other 2 patients had positive reactions to cocamidopropylamine and CAPB. Control participants had negative patch results.

Six out of the 7 original participants with dermatitis were patched tested with DMAPA along with controls on normal and tape-stripped skin at 0 ppm to 10 000 ppm. The participants were also tested with DMAPA in the presence of 0.2% aqueous, SLS, or in the presence of 1.0% pure CAPB (<0.3% cocamidopropylamine, <10 ppm DMAPA). The patch sites were again read on day 2 and day 4 after the patch applications. One of the 6 participants reacted to DMAPA on normal and tape-stripped skin at concentrations >1000 ppm. Three of the 6 participants reacted to DMAPA in the presence of SLS (1 at 10 000 ppm, 1 at 1000 to 10 000 ppm, and 1 at 100 to 10 000 ppm). None of the participants reacted to the 1.0% pure CAPB. The authors concluded that the sensitization experienced by the participants to the CAPB products was likely due to the residual intermediates from the CAPB production, with reaction to cocamidopropylamine more likely than DMAPA.[82] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

The impurities DMAPA and amidoamine in CAPB were further analyzed for sensitization potential in 10 participants with CAPB allergy.[83] The participants that had all tested positive to CAPB 1% aqueous (Firma type) were patch tested with CAPB 1% aqueous (Chemotechnique type), DMAPA 1% aqueous, and purified amidoamine at 0.5%, 0.25%, and 0.1% aqueous. All the participants had ++ reactions to DMAPA at 1% and purified amidoamine at 0.5%. Most participants also had ++ reactions to purified amidoamine at 0.25% and the remaining had + reactions to this concentration. Four patients had positive reactions (++) to the purified amidoamine at 0.1%. No reactions were observed to the CAPB from Chemotechnique, which was suggested to have a higher purity by the authors. Control patches in 20 volunteers were negative for amidoamine. The authors concluded that cross-reactivity between DMAPA and amidoamine causes CAPB allergy. They also suggested that DMAPA is the true sensitizing material and amidoamine aids in the trans-epidermal penetration of DMAPA. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

Brey and Fowler performed a retrospective study of patients that had positive patch test results to 1.0% aqueous CAPB and/or 1.0% amidoamine in the year 2001.[84] Reactions to other allergens were also recorded. Out of 957 patients patch tested in 2001, 49 had positive reactions to CAPB, amidoamine, or both. A follow-up evaluation in 35 patients was performed to establish relevance of reactions to CAPB and amidoamine with the use of products containing these chemicals. Fifteen patients (42.9%) reacted to CAPB, 12 patients (34.3%) reacted to amidoamine, and 8 patients (22.8%) reacted to both. Of the 35 patients, 29 (83%) could identify products containing CAPB at home. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

Fowler et al performed a retrospective study of patients with CAPB and/or amidoamine contact allergy in 2001.[111] Out of 975 patients, 15 had a positive patch test reaction to 1.0% CAPB only, 25 had a positive patch test reaction to 0.1% amidoamine only, and 18 had positive reactions to both (58 patients total). Definite and probable relevance (known exposure to CAPB) was determined in 16 patients that tested positive for amidoamine and in 16 that tested positive for

CAPB. This study also evaluated formaldehyde allergy. Of the 58 patients, 12.7% were also allergic to formaldehyde. This was compared to the 10.1% of the total 975 patients that had formaldehyde allergy. The authors suggested that there is no significant relationship between CAPB or amidoamine allergy and formaldehyde allergy. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

The NACDG evaluated 4913 patients for allergic contact dermatitis with an extended screening series of 65 allergens from January 1, 2001 to December 31, 2002. CAPB (1% aqueous) and the by-product of CAPB production, amidoamine (0.1% aqueous), were both included in this screening series. Positive results for CAPB were observed in 2.8% of the patients, while 2.3% were positive for amidoamine. The relevance of the CAPB and amidoamine reactions (present and past) was 90.9% and 85%, respectively.[112] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

In a study by Li to determine the sensitization rate of CAPB in China and to analyze the relationship between CAPB and DMAPA, 429 patients (105 male, 324 female; 9-81 years old) with suspected contact allergy were patch tested with 1% aqueous CAPB (purified) and 1% aqueous DMAPA.[113] The patients were also tested with the European standard series.

Of the 429 participants tested, 9 had irritant reactions, 12 had questionable reactions, and 42 had + reactions to CAPB. No reactions to CAPB greater than ++ were observed. Also of the 429 patients, 76 were diagnosed with cosmetic allergic contact dermatitis. Twenty-seven of these participants and 15 (out of 353) of the participants with cosmetic allergic contact dermatitis had positive reactions to CAPB ($P < .05$). Only 25 of the former and none of the latter had relevant reactions. Ten of the 429 patients had positive reactions to DMAPA, 8 of which were considered relevant. Six of the 10 patients also had positive reactions to CAPB. Because the participants of this study had positive reactions to both CAPB (purified) and DMAPA, the authors recommended that patch tests in cases of suspected cosmetic allergic contact dermatitis contain both CAPB and DMAPA.[113] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

Provocative Use Studies

A provocative use study of products containing CAPB was performed by Fowler et al.[114] Ten participants were identified through positive reactions to 1% aqueous CAPB in routine patch testing. Ten control participants negative to CAPB were also enrolled. The provocative use test was divided into 3 phases, with 3 different test products (shampoo, liquid hand soap, and body wash) used in each phase. The products were specially formulated with CAPB-F grade (active level of CAPB in shampoo was 5.0%; active level in hand soap and body wash was 5.2%). Phase I was a forearm wash test with the shampoo diluted to 10% in tap water. If no allergic reaction occurred in Phase I, participants then entered Phase II of the study: daily use of shampoo as hair cleanser. Participants proceeded to phase III of the study if no allergic reactions to the shampoo occurred. In phase III, the participants used the shampoo, body wash, and hand soap for 3 weeks.

At least 2 months after the product use tests, the participants were patch tested with CAPB grades F and S (both 1% aqueous), DMAPA (0.1% pet), amidoamine (0.1% aqueous), sodium monochloroacetate (0.1% aqueous), a proprietary mixture of preservatives for CAPB, and other potential allergens (perfumes and preservatives) that were in the test product formulations. Control participants were patched with 1% CAPB.

Three participants completed the product use phases without experiencing an allergic reaction. Seven participants had erythema, scaling, and pruritus on the arms, face, and/or neck in either phase I or II of the study. One participant that experienced a positive reaction in the first phase was asked to repeat the forearm use test with the CAPB-containing shampoo on the left arm and with a CAPB-absent shampoo on the right arm. The participant experienced a positive reaction on both arms, which was likely caused by the preservatives in the shampoo products (as shown through patch testing). In phase III, 3 participants had scalp, face, and/or neck and body dermatitis.

Patch testing was performed in 9 of the 10 participants, with 6 participants reacting to 0.1% amidoamine. Five of these 6 participants had positive reactions during the product use phases. Two participants had reactions to the CAPB-F grade with preservative, 3 had reactions to CAPB-F grade without preservative, 1 reacted to the CAPB-S grade, and 1 reacted to the proprietary preservative mixture. Two participants had questionable reactions to DMAPA. No other adverse reactions were noted in the participants. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

A follow-up patch test with 7 of the participants was performed using purified CAPB (containing only 1 ppm amidoamine), CAPB-F grade (with approximately 3000 ppm amidoamine), and 2 concentrations of amidoamine (0.1% and 0.01% aqueous). Two participants had questionable reactions to the purified CAPB, while there were 3 positive reactions to the CAPB-F grade, 4 positive reactions to the higher concentration of amidoamine, and 2 positive reactions to the lower concentration of amidoamine. The authors concluded that the impurity amidoamine may be the causative allergen in CAPB sensitivity and they recommend that cosmetics and personal care products should be formulated to minimize contamination with this impurity. In addition, the authors could not rule out the possibility that CAPB alone was not an allergen to presensitized individuals.[114,115]

Another provocative use test was conducted by Fartasch et al.[116] Participants with eczema were tested for CAPB allergy while undergoing patch testing for the standard allergen series. Out of 1063 patients, 13 were identified with a positive patch

reaction; however, relevance could only be established in 4 of the participants. Another 6 patients were referred to the study for eczematous eruptions of the scalp and/or hand dermatitis and had positive 1% aqueous CAPB patch test reactions. Twenty volunteers served as controls for the study.

The product use study consisted of 3 phases. In phase I, a 0.1 mL test sample of shower gel containing CAPB (25% dilution; DMAPA below 1 ppm) was applied, lathered for 1 minute, and rinsed on the participants' forearms twice daily for 7 days. The second phase of the study consisted of patch testing in order to differentiate irritant reactions from allergic reactions and to reconfirm the sensitivity to CAPB and DMAPA. The participants were patch tested with 0.1%, 0.3%, and 1.0% dilutions of CKKB (Tegobetaine CKKB5; 1.1 ppm DMAPA) and DMAPA, respectively. Patch sites were read on days 2, 3, and 4 following application. Participants that had no allergic reactions in phase I participated in phase III. In this phase, the participants used the shower gel as they would in normal daily hygiene practices for 4 weeks.

No skin irritation was observed in phase I of the study. One participant with a history of atopic dermatitis was removed from the study due to a flare. Another participant had an immediate "wheal like reaction" on days 3 and 6 that cleared within minutes. This participant continued the forearm test an extra week and had no further effect. In phase II, 1 control had an irritating reaction to 1% CAPB. In the study group, 5 out of the 10 participants had a positive reaction to 1% CAPB and another 3 had marginal and/or irritant reactions. One participant had a positive reaction to DMAPA but had no clear reaction to CAPB. Another participant that had a positive reaction to CAPB had a doubtful reaction to 1% DMAPA. Eight participants did not react to DMAPA. Only 7 participants participated in phase III of the study (the other 2 were not available), and no adverse reactions were observed in these participants. The authors concluded that CAPB as tested may be used safely in individuals with CAPB sensitivity.[116] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active.)

Case Reports

Several case studies of allergic contact dermatitis reported positive patch tests to amidoamine and DMAPA, with 1 study reporting DMAPA elicited reaction at concentrations of 0.1% and greater.[9,123-127]

Quantitative Risk Assessment

The Personal Care Products Council's Task Force on Sensitization Risk from CAPB Impurities used a quantitative risk assessment (QRA) approach developed by Api et al.[51] and the Research Institute for Fragrance Materials (RIFM)[117] to determine the levels of DMAPA and amidoamine impurities for which no sensitization should occur.[118] Based on the findings of LLNA and human sensitization studies on DMAPA and amidoamine described in this report, the Council's task force determined the conservative weight of evidence no expected sensitization induction levels (WoE NESIL) for DMAPA and amidoamine to be 425 $\mu g/cm^2$ and 180 $\mu g/cm^2$, respectively. When the level of impurities in raw CAPB materials is determined for product exposure (based on a typical exposure of 0.5% for amidoamine and 0.01% for DMAPA and estimated dose per unit area), a level of acceptable risk can be calculated for each cosmetic product category. These values are calculated based on sensitization assessment factors (SAFs), acceptable exposure levels (AELs = WoE NESIL $\times$ SAF^{-1}), and consumer exposure level (CEL) that are appropriate for each product category. According to the QRA method, the ratio of AEL $\times$ CEL^{-1} must be equal to or greater than 1 to ensure no sensitization to consumers. See Tables 9 and 10 for the breakdown of the values used in the calculations for this QRA. The QRA found that all of the product categories had acceptable levels of risk for exposure to DMAPA.

Using this approach, a ratio of less than 1 may result using the parameters given above, for example, with amidoamine in underarm deodorants (AEL $\times$ CEL^{-1} = 0.15). Such a finding could be addressed for such particular product applications by reducing the concentration of CAPB raw material in these finished products or choosing CAPB of higher purity when producing these products.

Summary

Cocamidopropyl betaine is a zwitterionic ammonium compound containing a moiety of either a saturated or unsaturated fatty acid ranging in length from 6 to 18 carbons in amide linkage with aminopropyl betaine. The source of these fatty acids, predominately lauric acid, is coconut oil. Other related ingredients are amidopropyl betaines with attached fatty acid moieties unique to the source, for example, sesame oil for sesamidopropyl betaine.

Cosmetic grade CAPB, an aqueous solution, normally contains 35% solids. The NaCl content of these solids ranges from 4.5% to 5.6%. The concentration, when expressed as activity, is determined by subtracting the percentage NaCl from the percentage total solids. Because of uncertainty in whether concentrations given are active or dilutions of an active cosmetic grade material, in some cases the actual concentration of CAPB or other tested material is not known, but it appears that any uncertainty would not be greater than a factor of 3. No *N*-nitroso compounds were detected in samples of commercially supplied CAPB analyzed by gas chromatography–thermal energy analysis.

CAPB is used primarily as an amphoteric surfactant in shampoos, conditioners, and other cleansing preparations. It was listed as an ingredient in 2460 cosmetic formulations voluntarily reported to FDA. Reported use concentrations range from 0.2% to 25%.

The oral LD_{50} of full-strength commercial samples of 30% active CAPB was 4.91 g/kg in CFR mice and 7.45 mL/kg in Wistar rats. Another study of 30% active CAPB in Wistar rats

Table 9. Quantitative Risk Assessment of Amidoamine (AA) in Cosmetic Products Containing CAPB[a,b,118]

Product Category	% Max Concentration of Use (active)	% Activity f Raw Material	Product Exposure[c] (μg/cm²)	CAPB Exposure (μg/cm²)	AA CEL (μg/cm²)	SAF	AA AEL	AA AEL/CEL
Baby shampoo	4	30	200	26.67	0.13	100	1.80	13.50
Other baby products	6	30	10	2.00	0.01	100	1.80	180.00
Bath oils, tablets and salts	7	30	10	2.33	0.01	100	1.80	154.29
Bubble baths	6	30	10	2.00	0.01	100	1.80	180.00
Bath capsules	0.9	30	10	0.30	0.00	100	1.80	1200.00
Other bath preparations	6	35	10	1.71	0.01	100	1.80	210.00
Eye shadow	2.5	35	2170	155.00	0.78	300	0.60	0.77
Eye makeup remover	0.005	1	900	4.50	0.02	100	1.80	80.00
Hair conditioners	4	35	200	22.86	0.11	100	1.80	15.75
Hair sprays (aerosol fixatives)	0.2	36	1390	7.72	0.04	100	1.80	46.62
Hair straighteners	0.7	36	4200	81.67	0.41	100	1.80	4.41
Permanent waves	2	35	4200	240.00	1.20	100	1.80	1.50
Rinses (noncoloring)	9	30	170	51.00	0.26	100	1.80	7.06
Shampoos (noncoloring)	9	38	170	40.26	0.20	100	1.80	8.94
Tonics, dressings and other hair grooming aids	4.5	30	990	148.50	0.74	100	1.80	2.42
Hair dyes and colors[d]	6	30	1000	200.00	1.00	100	1.80	1.80
Hair tints[d]	6	30	990	198.00	0.99	100	1.80	1.82
Hair rinses (coloring)	6	30	200	40.00	0.20	100	1.80	9.00
Hair color sprays (aerosol)	6	30	1390	278.00	1.39	100	1.80	1.29
Hair lighteners with color[d]	6	30	1000	200.00	1.00	100	1.80	1.80
Hair bleaches[d]	6	30	1000	200.00	1.00	100	1.80	1.80
Other hair coloring preparations	3	30	1000	100.00	0.50	100	1.80	3.60
Other manicuring preparations	0.8	39	970	19.90	0.10	100	1.80	18.09
Dentifrices (aerosol, liquid, pastes, and powders)	6	Not reported	1290	NA	NA	100	1.80	NA
Bath soaps and detergents	10	34	15	4.41	0.02	100	1.80	81.60
Deodorants (underarm)	1.6	31	7500	387.10	1.94	300	0.60	0.31
Douches	3.8	30	1380	174.80	0.87	100	1.80	2.06
Other personal cleanliness products	10	36	10	2.78	0.01	100	1.80	129.60
Shaving cream (aerosol, brushless, and lather)	9	35	70	18.00	0.09	300	0.60	6.67
Shaving soaps (cakes, sticks, etc)	9	30	70	21.00	0.11	300	0.60	5.71
Other shaving preparations	11	32	70	24.06	0.12	300	0.60	4.99
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	6.9	31	900	200.32	1.00	100	1.80	1.80
Body and hand creams, lotions, and powders	3	35	4200	360.00	1.80	300	0.60	0.33
Foot powders and sprays	4	30	2200	293.33	1.47	100	1.80	1.23
Paste masks (mud packs)	0.2	35	4200	24.00	0.12	100	1.80	15.00

[a] Assumptions in table above: AA @ 0.5% of CAPB; AA NESIL = 180 μg/cm².
[b] Shaded rows indicate the ratio of AEL × CEL^{-1} is less than 1.
[c] These data are derived from RIFM. It is advisable that formulators use experimentally determined exposure data when available.
[d] Note that these product categories may be diluted prior to application, such that maximum CAPB activity in finished product is 3%.

found the acute oral LD_{50} to be 8.55 g/kg. The oral LD_{50} of 30% active CAPB in albino rats of an unspecified strain was 4.9 g/kg. The acute oral LD_{50} for 35.61% active CAPB was >1.8 g/kg for male Sprague-Dawley rats. All female rats in this study died before study end. The acute oral LD_{50} was greater than 5.0 g/kg and the acute lethal dermal dose was greater than 2.0 g/kg in studies of CAPB (31% active) with CD rats.

In a 28-day short-term study in which groups of 8 male and female animals received 0, 100, 500, or 1000 mg/kg of 30% active CAPB, treatment-induced lesions were produced in the nonglandular portion of the stomach in the high-dose groups. Both males and females of the low-dose (100 mg/kg) group were comparable to concurrent controls.

In another 28-day oral toxicity study, rats received 0, 250, 500, or 1000 mg/kg of an unknown concentration of CAPB. In the 1000 mg/kg dose group, compound-related edema of the mucosa of the nonglandular stomach was observed at macroscopic examination and acanthosis of the mucosa, inflammatory edema of the submucosa, and multiple ulcerations were observed during microscopic examination. These effects were thought to be the result of the irritating properties of CAPB and not of systemic toxicity. The NOEL and LOEL for this study were 500 and 1000 mg/kg per d, respectively.

A subchronic oral toxicity study of an unknown concentration of CAPB rats that received 0, 250, 500, or 1000 mg/kg per d CAPB concluded that the NOEL was 250 mg/kg per d. Gastritis

Table 10. Quantitative Risk Assessment of 3,3-Dimethylaminopropylamine (DMAPA) in Cosmetic Products Containing CAPB[a,118]

Product Category	% Max Concentration of Use (active)	% Activity of Raw Material	Product Exposure[b] (μg/cm²)	CAPB Exposure (μg/cm²)	DMAPA CEL (μg/cm²)	SAF	DMAPA AEL	DMAPA AEL/CEL
Baby shampoo	4	30	200	26.67	0.0027	100	4.25	1593.75
Other baby products	6	30	10	2.00	0.0004	100	4.25	10625.00
Bath oils, tablets, and salts	7	30	10	2.33	0.0005	100	4.25	9107.14
Bubble baths	6	30	10	2.00	0.0004	100	4.25	10625.00
Bath capsules	0.9	30	10	0.30	0.0001	100	4.25	70833.33
Other bath preparations	6	35	10	1.71	0.0003	100	4.25	12395.83
Eye shadow	2.5	35	2170	155.00	0.0310	300	1.42	45.70
Eye makeup remover	0.005	1	900	4.50	0.0009	100	4.25	4722.22
Hair conditioners	4	35	200	22.86	0.0046	100	4.25	929.69
Hair sprays (aerosol fixatives)	0.2	36	1390	7.72	0.0015	100	4.25	2751.80
Hair straighteners	0.7	36	4200	81.67	0.0163	100	4.25	260.20
Permanent waves	2	35	4200	240.00	0.0480	100	4.25	88.54
Rinses (noncoloring)	9	30	170	51.00	0.0102	100	4.25	416.67
Shampoos (noncoloring)	9	38	170	40.26	0.0081	100	4.25	527.78
Tonics, dressings and other hair grooming aids	4.5	30	990	148.50	0.0297	100	4.25	143.10
Hair dyes and colors[c]	6	30	1000	200.00	0.0400	100	4.25	106.25
Hair tints[c]	6	30	990	198.00	0.0396	100	4.25	107.32
Hair rinses (coloring)	6	30	200	40.00	0.0080	100	4.25	531.25
Hair color sprays (aerosol)	6	30	1390	278.00	0.0556	100	4.25	76.44
Hair lighteners with color[c]	6	30	1000	200.00	0.0400	100	4.25	106.25
Hair bleaches[c]	6	30	1000	200.00	0.0400	100	4.25	106.25
Other hair coloring preparations	3	30	1000	100.00	0.0200	100	4.25	212.50
Other manicuring preparations	0.8	39	970	19.90	0.0040	100	4.25	1067.98
Dentifrices (aerosol, liquid, pastes, and powders)	6	Not reported	1290	NA	NA	100	4.25	NA
Bath soaps and detergents	10	34	15	4.41	0.0009	100	4.25	4816.67
Deodorants (underarm)	1.6	31	7500	387.10	0.0774	300	1.42	18.30
Douches	3.8	30	1380	174.80	0.0350	100	4.25	121.57
Other personal cleanliness products	10	36	10	2.78	0.0006	100	4.25	7650.00
Shaving cream (aerosol, brushless, and lather)	9	35	70	18.00	0.0036	300	1.42	393.52
Shaving soaps (cakes, sticks, etc)	9	30	70	21.00	0.0042	300	1.42	337.30
Other shaving preparations	11	32	70	24.06	0.0048	300	1.42	294.37
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	6.9	31	900	200.32	0.0401	100	4.25	106.08
Body and hand creams, lotions and powders	3	35	4200	360.00	0.0720	300	1.42	19.68
Foot powders and sprays	4	30	2200	293.33	0.0587	100	4.25	72.44
Paste masks (mud packs)	0.2	35	4200	24.00	0.0048	100	4.25	885.42

[a] Assumptions in table above: DMAPA @ 0.01% of CAPB; DMAPA NESIL = 425 μg/cm².
[b] These data are derived from RIFM. It is advisable that formulators use experimentally determined exposure data when available.
[c] Note that these product categories may be diluted prior to application, such that maximum CAPB activity in finished product is 3%.

of the forestomach was observed in rats in the 500 and 1000 mg/kg per d dose groups.

Topical administration of varying commercial grades of CAPB (7.5%-30% activity) in single insult occlusive patch tests involving rabbits resulted in PIIs ranging from 0 to 3.75 (maximum score = 8). Slight edema was observed with CAPB with a 10% activity but not with CAPB with a 7.5% activity.

No evidence of delayed contact hypersensitivity was found in Pirbright white guinea pigs topically administered solutions of 10% active CAPB in a Magnusson-Kligman maximization test. Microscopic changes in the treated skin of albino guinea pigs indicated slight delayed-type contact sensitization by a 3.0% active CAPB solution in a maximization test and modified Draize test.

Maximum mean irritation scores for eyes of rabbits treated with 30% active CAPB and left unrinsed ranged from 26 to 42 (maximum score = 110). Score for rinsed eyes ranged from 2 to 10. Irritation was observed primarily in the conjunctivae of treated eyes. At 4.5% active CAPB, there was slight conjunctival irritation in unrinsed eyes and very slight irritation in rinsed eyes. Scores for product formulations containing 2.2% to 6.3% active CAPB ranged from 4 to 30 in unrinsed, treated eyes of rabbits and were 3.3 and 20.0 in rinsed, treated eyes of rabbits.

The mutagenic potential of 30.9% and 31.0% active CAPB formulations was tested in the *Salmonella*/mammalian microsome mutagenicity assay and the L5178Y TK +/− mouse lymphoma assay. CAPB was nonmutagenic in these assays.

CAPB was not mutagenic to the *S typhimurium* indicator organisms in Ames *Salmonella*/microsome reverse mutation assays and in a mouse micronucleus assay.

In a single insult occlusive patch test of a 1.0% aqueous dilution of a product formulation containing 6.3% active CAPB, no skin irritation was observed in 15 of 19 human participants; 4 of the participants had slight irritation. Slight erythema was observed after occlusive patching of 12 participants with an 8% aqueous dilution of a soap formulation containing 2.0% active CAPB daily for 5 days. Two soap formulations containing 2.25% active CAPB were considered primary irritants after a 21-day consecutive occlusive patch study.

A formulation containing almondamidopropyl betaine and olivamidopropyl betaine (both at 0.005% active concentration) was not a primary skin sensitizer or skin irritant in 103 participants. A formulation containing capryl/capramidopropyl betaine at 1.72% active concentration was not a skin sensitizer in 26 participants. No dermal irritation or allergic contact sensitization was reported in studies of formulations containing 0.42%, 0.7%, or 0.03955% active lauramidopropyl betaine. Formulations containing shea butteramidopropyl betaine were not sensitizing in studies of 0.04% or 0.54% active concentration.

An additional study investigated the potential of a 3.0% active solution of CAPB to induce contact photoallergy. There was no response to the challenge tests except for those exposed to both UVA and UVB radiation, who had mild to moderate erythemic responses that were not uncommon and were said to have resulted from the sunburn derived from UVB exposure.

CAPB was not a skin sensitizer at 1% in a study of 100 volunteers or in another study at 1.5% in 141 volunteers. Clinical sensitization studies and case studies show that persons already sensitized to CAPB react to concentrations of 1.0% of the material in water. Several case reports have found patients reporting contact allergy to multiple types of personal care products, including shampoos, contact lens solutions, eye makeup remover, bath gels, and toothpaste. Researchers have included the CAPB impurities, DMAPA and amidoamine, in the scope of sensitization and case studies and have found that one or both of the impurities may be the responsible agent for contact allergy to CAPB. QRAs of these impurities may be performed to ensure acceptable levels of risk in consumers.

Discussion

While very few toxicity studies were identified specifically for the additional amidopropyl betaines (with R groups representing fatty acids derived from a source other that coconut oil) that were added to this safety assessment, there is no reason to expect these ingredients to differ in toxicity from CAPB. The amidopropyl betaines appear to be manufactured in the same manner as CAPB, with the difference only being in the fatty acid composition of the oil that is the source of the R group. Some of these fatty acid compounds have already been reviewed by the Panel and have been found to be safe for use in cosmetic ingredients. The Panel noted gaps in the available safety data for some of the amidopropyl betaines in this safety assessment. The available data on many of the ingredients are sufficient, however, and similarity between structural activity relationships and biologic functions in cosmetic concentrations of use and can be extrapolated to support the safety of the entire group. Therefore, the Panel determined that the toxicity data on CAPB could be read across to include:

- almondamidopropyl betaine,
- apricotamidopropyl betaine,
- avocadamidopropyl betaine,
- abassuamidopropyl betaine,
- behenamidopropyl betaine,
- canolamidopropyl betaine,
- capryl/capramidopropyl betaine,
- coco/oleamidopropyl betaine,
- coco/sunfloweramidopropyl betaine,
- cupuassuaidopropyl betaine,
- isostearmidopropyl betaine,
- lauramidopropyl betaine,
- meadowfoamamidopropyl betaine,
- milkamidopropyl betaine,
- minkamidopropyl betaine,
- myristamidopropyl betaine,
- oatamidopropyl betaine,
- oleamidopropyl betaine,
- olivamidopropyl betaine,
- palmamidopropyl betaine,
- palmitamidopropyl betaine,
- palm kemelamiodpropyl betaine,
- ricinoleamidopropyl betaine,
- sesamidopropyl betaine,
- shea butteramidopropyl betaine,
- soyamidopropyl betaine,
- stearamidopropyl betaine,
- tallowamidopropyl betaine,
- undecyleneamidopropyl betaine, and
- wheat germamidopropyl betaine.

In reviewing studies involving CAPB and related ingredients, often the percentage of active material in the test material was clearly stated; but in other cases, it was not clear whether the test material was active material or a dilution of active material. Because the difference, at most, would be a factor of 3, the uncertainty was factored into the review process.

The Panel considered that the available acute, short-term, and subchronic animal toxicity studies were supportive of the safety of CAPB. In vitro genotoxicity studies supported the absence of mutagenic activity. The Panel noted the absence of reproductive and developmental toxicity and absorption data but also noted that CAPB did not produce systemic toxicity in a 92-day oral toxicity study in rats. Because these ingredients are very large molecular weight structures and water soluble, the Panel concluded that they would not be readily absorbed into the skin.

In the absence of inhalation toxicity data, the Panel determined that CAPB can be used safely in hair sprays, because the product particle size was not respirable. The Panel reasoned that the particle size of aerosol hair sprays (~38 μm) and pump hair sprays (>80 μm) was large compared to respirable particulate sizes (≤10 μm).

In past ingredient safety assessments, the Panel had expressed concern over *N*-nitrosation reactions in ingredients containing amine groups. CAPB, and the other betaine ingredients in this assessment, contain secondary amides that may serve as substrates for *N*-nitrosation. Additionally, these ingredients may contain secondary amine impurities which may serve as substrates for *N*-nitrosation. Therefore, the Panel recommended that these ingredients should not be included in cosmetic formulations containing *N*-nitrosating agents.

The Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

The Panel considered the dangers inherent in using animal-derived ingredients, namely the transmission of infectious agents. While tallow may be used in the manufacture of some ingredients in this safety assessment and is clearly animal derived, the Panel noted that tallow is highly processed and tallow derivatives even more so. The Panel agreed with determinations by the FDA that tallow derivatives are not risk materials for transmission of infectious agents.

While CAPB and the related amidopropyl betaines were noted to be dermal irritants, the primary concern was related to the presence of impurities that were found to be dermal sensitizers. The Panel recognized that these ingredients can have the potential to induce skin sensitization, most likely due to the impurities DMAPA and fatty acid amidopropyl dimethylamine (amidoamine). Thirteen studies of CAPB and related amidopropyl betaines on normal human skin at use concentrations indicated no sensitization induced by these cosmetic ingredients. A QRA on DMAPA at a concentration of 0.01% in raw CAPB indicated no sensitization in finished cosmetic products; amidoamine at a concentration of 0.5% in raw CAPB may cause sensitization in certain finished cosmetic products. The Panel concluded that skin sensitization is not a concern with the use of CAPB and related amidopropyl betaines as currently used in cosmetic products when a QRA is performed to demonstrate that concentration, product type, and product usage will not produce exposures that could induce sensitization. The Panel advises industry to continue minimizing the concentrations of the sensitizing impurities.

Conclusion

The CIR Expert Panel concluded that the following ingredients are safe in cosmetics as long as they are formulated to be nonsensitizing, which may be based on a QRA

- cocamidopropyl betaine,
- almondamidopropyl betaine,
- apricotamidopropyl betaine*,
- avocadamidopropyl betaine*,
- babassuamidopropyl betaine,
- behenamidopropyl betaine*,
- canolamidopropyl betaine*,
- capryl/capramidopropyl betaine,
- coco/oleamidopropyl betaine,
- coco/sunfloweramidopropyl betaine*,
- cupuassuamidopropyl betaine*,
- isostearamidopropyl betaine*,
- lauramidopropyl betaine,
- meadowfoamamidopropyl betaine*,
- milkamidopropyl betaine*,
- minkamidopropyl betaine*,
- myristamidopropyl betaine,
- oatamidopropyl betaine,
- oleamidopropyl betaine*,
- olivamidopropyl betaine,
- palmamidopropyl betaine*,
- palmitamidopropyl betaine*,
- palm kernelamidopropyl betaine,
- ricinoleamidopropyl betaine*,
- sesamidopropyl betaine*,
- shea butteramidopropyl betaine,
- soyamidopropyl betaine,
- stearamidopropyl betaine*,
- tallowamidopropyl betaine*,
- undecyleneamidopropyl betaine, and
- wheat germamidopropyl betaine*.

Were ingredients in this group not in current use (identified with an *) 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.

Authors' Note

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

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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: October 24, 2012

SUBJECT: Unpublished Data: Product Containing Oleamidopropyl Dimethylamine

Product Investigations, Inc. 2003. Single patch test summary: Oleamidopropyl Dimethylamine 1% Oil. Report No. 17227.

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PRODUCT INVESTIGATIONS, INC.

151 East Tenth Avenue
Conshohocken, PA 19428
610-825-5855 • fax 610-825-7288

SINGLE PATCH TEST SUMMARY

Oleamidopropyl Dimethylamine 1% Oil'

Study Objective To confirm skin compatibility.

Method Single application of 10% dilution of material under semi-occluded patch for 48 hours, then evaluation of skin condition with ranking, under dermatological supervision.

Investigator Moms V. Shelanski, MD.CM

Application site L2

Number of subjects 100

Panel description Male and Female, 18 to 70 years of age inclusive.

Conclusion Under the conditions of the study, skin compatibility is considered to be:

Very good	☑
Good	☐
Moderate	☐
Poor	☐

for this product category

Morris V. Shelanski, MD.CM

Morris V. Shelanski, MD.CM

11 November 2003

Date

PRODUCT INVESTIGATIONS,INC.

151 East Tenth Avenue
Conshohocken, PA 19428
610-825-5855 • fax 610-825-7288

REPORT: PII Nº 17227

DETERMINATION OF THE PRIMARY IRRITATING PROPENSITIES OF Oleamidopropyl Dimethylamine 1% oil, SAMPLE#U03432.02 ON HUMAN SKIN

6 November 2003

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DETERMINATION OF THE PRIMARY IRRITATING PROPENSITIES OF Oleamidopropyl Dimethylamine 1% oil SAMPLE #U03432.02 ON HUMAN SKIN

1.00 OBJECTIVE:

To determine whether use study Oleamidopropyl Dimethylamine 1% oil **SAMPLE#U03432.02** is capable of eliciting visible skin damage during a forty-eight-hour period of contact.

2.00 FEATURES:

.10 An application of forty-eight hours continuous contact on intact human skin was to be conducted under double blind conditions on a shared panel composed of one hundred or more subjects at the outset.

.20 The contact site was to be examined and graded upon removal of the patches (forty-eight hours after application was begun) and 24-hours later.

.30 This study was conducted in compliance with the standards of good clinical practices generally applicable for the protection of the privileges and well-being of individuals who participate in patch test procedures.

3.00 SPONSOR:

Project Director: Christine K. Wood, CRA, Dept. of Biological Sciences

4.00 AUTHORIZATION: Letter dated 16 October 2003 from Christine K. Wood

5.00 STUDY PRODUCT:

Identification:	Oleamidopropyl Dimethylamine 1% oil
Sample #:	**U03432.02**
Type of product:	Hair Treatment
Received:	17 October 2003
PI N°:	17227
Form used in study:	10% aqueous preparation

6.00 SITE OF STUDY: Product Investigations, Inc.
151 East Tenth Avenue
Conshohocken, PA 19428

Study Personnel:

Medical Director:	Morris V. Shelanski, MDCM
Study Supervisor:	Joseph E. Nicholson III
Chief Technician:	June Zummo
Quality Assurance:	Samuel J. Charles III

7.00 DATES OF STUDY:

Started:	28 October 2003
Completed:	31 October 2003

8.00 INFORMED CONSENT:

This document, which each candidate had to read and sign before being entered into the study, was all encompassing and presented the following information to prospective subjects:

a) why the study was being performed;
b) how the study was to be performed;
c) that subjects were not to expect any benefits to health or well-being from exposure to the product;
d) that there were risks to well-being that would be incurred by participants;
e) what commitments and clinic visits a person accepted as a subject would have to make; and
f) what considerations the subject would be entitled to receive and the conditions for receiving them.

9.00 SELECTION OF SUBJECTS:

One hundred and two adults who qualified in accordance with the following criteria were selected for participation.

.10 Inclusion Criteria: Satisfaction of all the following items was obligatory:

a) The candidate was at least eighteen years of age and in good general health, and
b) agreed to comply fully with the scheduled study regimen, and
c) expressed awareness that participation involved risks to her/his well-being, and
d) denied that a need for money had induced her/him to participate against her/his better judgement, and
e) had read the informed consent statement and signed it willingly and without reservation.

.20 Exclusion Criteria: Any one of the following items was cause for rejection:

a) The candidate had an illness that contraindicated participation; or
b) had skin that was unsuitable for use in this study; or
c) had a documented history of significant intolerance to the category of products submitted for study; or
d) was using medications that could enhance or suppress tolerance for a skin irritant or sensitizer; or
e) was a female who was pregnant or was breast feeding an infant.

10.00 DEDICATION:

The subjects were engaged exclusively in the study of products submitted

11.00 SITE ASSIGNMENT:

Oleamidopropyl Dimethylamine 1% oil , SAMPLE#U03432.02 was assigned site L2 on the left upper back of each subject.

12.00 PATCHING DEVICES:

Partially-occlusive patching devices were initially used to convey the product to the skin and to maintain it on its assigned site on each subject. These devices consist of a *2* cm x *2* cm absorbent pad centered on the adhesive-coated surface of a 4 cm x *2* cm plastic film.

13.00 PREPARATION OF A PATCHING DEVICE:

The webril pad of a patching device was infused with approximately 150µl of a 10% aqueous preparation of the study product.

14.00 TECHNIQUE FOR APPLYING A PATCHING DEVICE:

.10 A prepared device was positioned on its designated site on each subject with the study sample-treated surface of the pad in contact with the skin.
.20 Firm pressure was applied to the backing of the device to effect intimate contact of the pad with the skin and to bond the flanges of the device securely to the skin.

15.00 TECHNIQUE FOR REMOVING A PATCHING DEVICE:

.10 The device was scheduled to be removed in the clinic by an experienced technician after forty-eight hours.
.20 The patching device and product were removed as gently as circumstances permitted.

16.00 GRADING PROCEDURE:

The site exposed to the product was examined and graded forty-eight hours following initiation of the application and again twenty-four hours after the patch was removed in accordance with the following scale.

Morphology	Visible Change	Grade
None or subclinical changes	None	0
Vascular dilatation:	Faint redness with poorly defined margins	1
	moderate to intense redness, well-defined margins	2
Vascular leakage, infiltration:	redness plus well-defined edema	3
	redness plus papules, or vesicles or ulceration	4

DAY 1

Tuesday

1. When a subject presented herself/himself at the clinic, the skin of the contact site assigned to the product submitted for study was examined and ascertained to be suitable before approval was given for the applications to begin.

2. A partially occlusive patching device, freshly infused with 150μl of the study product solution, was applied on its designated contact site.

3. The skin around the device was marked.

4. The subject was instructed to return at the same time on the next day and dismissed.

DAY 2

Wednesday

1. When a subject returned to the clinic, the patch was examined to ascertain whether it was maintaining good contact on its assigned site.

2. The marks identifying the location of the contact site were reinforced.

3. The subject was instructed to return at the same time on the next day and dismissed.

DAY 3

Thursday

1. When a subject returned, the marks identifying the location of the contact site were reinforced.

2. The patch was removed, the contact site was examined and graded. (cf. Section 16.00)

3. The subject was instructed to return at the same time on the next day and dismissed.

DAY 4

Friday

1. When a subject returned, the marks identifying the location of the contact site were reinforced.

2. The contact site was examined and graded.

3. The subject was dismissed from the study with instructions to notify the investigator immediately should the skin of the contact site manifest any change for the worse during the ensuing weeks.

18.00 COMPLIANCE:

All of the 102 subjects who received the test material complied with the study regimen.

19.00 SUMMARY OF RESULTS:

.10 No complaint was volunteered by any of the subjects when they returned for inspection of the patches twenty-four hours after they were first applied.

.20 No adverse effect was detected on any of the 102 subjects who participated in this study.

20.00 SIGNIFICANCE OF THE FINDINGS:

The absence of responses characterizes the product as one which is devoid of any clinically significant primary irritating propensities that can be detected under the prevailing study conditions.

21.00 CONCLUSION:

The data do not contraindicate non-occlusive usages entailing uninterrupted exposure of the skin to this product for periods up to forty-eight hours in duration.

PRODUCT INVESTIGATIONS, INC.

7 November 2003
Date

Morris V. Shelanski, MDCM

22.00 QUALITY ASSURANCE REVIEW:

I have reviewed the data presented in this report and have found them to be accurate transcriptions of the raw data acquired during the course of this study.

11/6/03
Date

Samuel J. Charles III
Director, Quality Assurance

48-HOUR PATCH TEST

Sample U03432.02
Site: L2

PI-17227

Subj. #	Tues.	Wed.	Thurs.	Fri.
1	B	[redacted]	0	0
2	B		0	0
3	B		0	0
4	B		0	0
5	B		0	0
6	B		0	0
7	B		0	0
8	B		0	0
9	B		0	0
10	B		0	0
11	B		0	0
12	B		0	0
13	B		0	0
14	B		0	0
15	B		0	0
16	B		0	0
17	B		0	0
18	B		0	0
19	B		0	0
20	B		0	0
21	B		0	0
22	B		0	0
23	B		0	0
24	B		0	0
25	B		0	0
26	B		0	0
27	B		0	0
28	B		0	0
29	B		0	0
30	B		0	0
31	B		0	0
32	B		0	0
33	B		0	0
34	B		0	0
35	B		0	0
36	B		0	0
37	B		0	0
38	B		0	0
39	B		0	0
40	B		0	0
41	B		0	0
42	B		0	0
43	B		0	0

Subj. #	Tues.	Wed.	Thurs.	Fri.
44	B	[redacted]	0	0
45	B		0	0
46	B		0	0
47	B		0	0
48	B		0	0
49	B		0	0
50	B		0	0
51	B		0	0
52	B		0	0
53	B		0	0
54	B		0	0
55	B		0	0
56	B		0	0
57	B		0	A
58	B		0	0
59	B		0	0
60	B		0	0
61	B		0	0
62	B		0	0
63	B		0	0
64	B		0	0
65	B		0	0
66	B		0	0
67	B		0	0
68	B		0	0
69	B		0	0
70	B		0	0
71	B		0	0
72	B		0	0
73	B		0	0
74	B		0	A
75	B		0	0
76	B		0	0
77	B		0	0
78	B		0	0
79	B		0	0
80	B		0	0
81	B		0	0
82	B		0	0
83	B		0	0
84	B		0	0
85	B		0	0
86	B		0	0

48-HOUR PATCH TEST

Sample **U03432.02**
Site: L2

PI-17227

Subj. #	Tues.	Wed.	Thurs.	Fri.
87	B		0	0
88	B		0	0
89	B		0	0
90	B		0	0
91	B		0	0
92	B		0	0
93	B		0	0
94	B		0	0
95	B		0	0
96	B		0	0
97	B		0	0
98	B		0	0
99	B		0	0
100	B		0	0
101	B		0	0
102	B		0	0

Subj. #	Tues.	Wed.	Thurs.	Fri.

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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: September 6, 2012

SUBJECT: Comments on the Draft Report on the Fatty Acid Amidopropyl Dimethylamine Ingredients Prepared for the September 10-11, 2012 CIR Expert Panel Meeting

Key Issues

Abstract and Conclusion - CIR staff should not be writing conclusions for the CIR Expert Panel before the CIR Expert Panel has had a chance to vote on the conclusions. If CIR staff does write a conclusion for the CIR Expert Panel before the Panel has voted, at a minimum, the Abstract and Conclusion should be marked **"DRAFT"**.

Generally, in CIR reports new information is discussed in the text, while information from old reports is presented in tables. In this report, the new information is presented in tables, while the information from the CAPB report is presented in the text (this text from the CAPB report is about half of the text included in the report). The studies on the fatty acid amidopropyl dimethylamine ingredients that were included in the CAPB report should be summarized in the tables with the new information. The studies on DMAPA from the CAPB report should be put in a new table. The studies of CAPB itself are not necessary for this report.

The reader of the report in the current form expects that all of the irritation and sensitization data on the fatty acid amidopropyl dimethylamine ingredients are summarized in Table 5. This is not correct, as there are a number of helpful studies, e.g., studies described on p.4-5, and 6, on these ingredients only summarized in the information taken from the CAPB report.

Additional Comments

p.3 - It is misleading to state that "These ingredients" are used at concentrations up to 2%. Only Stearamidopropyl Dimethylamine was reported to be used in spray products at concentrations up to 2%. Oleamidopropyl Dimethylamine was reported to be used at a maximum of 0.15% in spray products.

p.3 - Please correct the spelling of "stearmidopropyl"

p.10 - The meaning of CKKB is not clear.

p.12 - The Summary should also mention the studies on the fatty acid amidopropyl dimethylamine ingredients that were presented in the CAPB report.

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p.13 - In the Discussion, it would be helpful to provide more details about the sensitization data, such as the fact that an HRIPT (n=104) was completed with an undiluted hair conditioner containing 2% Stearamidopropyl Dimethylamine (resulting in an estimated Stearamidopropyl Dimethylamine dose of 1000 $\mu g/cm^2$) and the hair conditioner was not a sensitizer.

p.13 - In the Conclusion, the ingredients with no reported uses still need to be marked with an asterisk.

p.24, Table 4 - Please correct the spelling of "Behanmidopropyl"

p.25, Table 5 - For reference 81, please indicate that the material tested was a hair conditioner containing 2% Stearamidopropyl Dimethylamine.