
Safety Assessment of Fatty Acid Amidopropyl Dimethylamines as Used in Cosmetics

Status: Draft Final Report for Panel Review
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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, Senior Scientific Analyst/Writer; Ivan Boyer, Ph.D., Toxicologist CIR; and Bart Heldreth, Ph.D., Chemist CIR.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: May 16, 2014
Subject: Draft Final Report on Fatty Acid Amidopropyl Dimethylamines

At the March 2014 meeting, the Panel issued a tentative safety assessment for public comment with the conclusion that the 24 fatty acid amidopropyl dimethylamines ingredients are safe in cosmetics when they are formulated to be non-sensitizing. The Panel noted that the impurity DMAPA in oleamidopropyl dimethylamine appeared to be present at a concentration higher than the DMAPA concentrations reported in other amidopropyl dimethylamines and, based on the data submitted, can exceed the limit recommended for DMAPA in “raw” CAPB (as supplied to formulators) by the Panel in the CAPB safety assessment. The Panel requested that industry provide additional information on DMAPA in oleamidopropyl dimethylamine.

The Panel also noted that, for stearamidopropyl dimethylamine, the highest reported maximum use concentration in leave-on products may yield DMAPA concentrations that exceed the Panel’s recommended limit for this impurity in “raw CAPB. Industry agreed with the Panel’s request to provide a QRA for stearamidopropyl dimethylamine, which includes the derivation of a WoE NESIL of 1000 $\mu\text{g}/\text{cm}^2$ from the safety test data presented in this safety assessment report.

Since the March meeting, we have received the QRA that was performed by the Council’s CIR Science and Support Committee. This data has been incorporated into the safety assessment. It should be noted that the QRA does not support the use of stearamidopropyl dimethylamine at current use levels in many product categories. Additionally, the VCRP data has been updated for 2014; no other new data have been received, including the requested data on DMAPA levels in oleamidopropyl dimethylamine. Comments that were received from the Council prior to the March meeting, as well as those on the tentative safety assessment, have been considered. The comments and the full data submission on the QRA are available for your review in this report package.

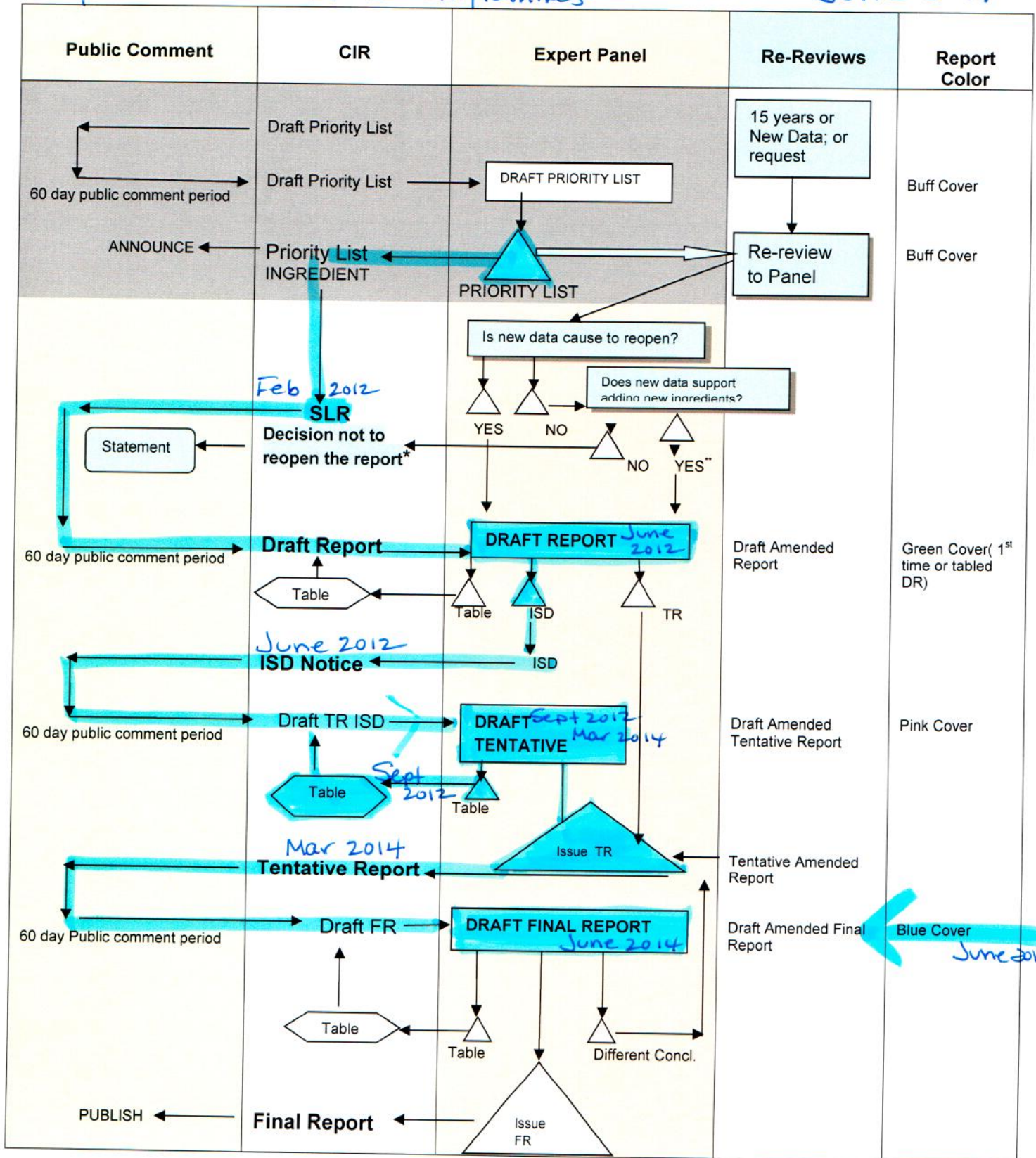
As a reminder, the CIR published the safety assessment of CAPB and its related amidopropyl betaines with the conclusion “safe in cosmetics as long as they are formulated to be non-sensitizing, which may be based on a QRA”. The two major impurities which were associated with sensitization in CAPB and related amidopropyl betaines were DMAPA and fatty acid amidopropyl dimethylamine (“amidoamine” when referring specifically to CAPB). The Panel issued the tentative safety assessment on fatty acid amidopropyl dimethylamines with the conclusion that these ingredients are safe when formulated to non-sensitizing, but did not include, explicitly, a statement about using a QRA to ensure that non-sensitizing concentrations are used. For consistency, should this report also mention that QRA may be used for this purpose?

The Panel should carefully review the abstract, discussion, and conclusion of this report and issue a Final Safety Assessment.

SAFETY ASSESSMENT FLOW CHART

Fatty Acid AmidoPropyl Dimethylamines

June 2014



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

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



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 and 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.

March 2014 - At the March 2014 meeting, the Panel issued a tentative safety assessment for public comment with the conclusion that the 24 fatty acid amidopropyl dimethylamines ingredients are safe in cosmetics when they are formulated to be non-sensitizing. The Panel noted that DMAPA impurities in oleamidopropyl dimethylamine appeared to be present at a concentration higher than the DMAPA concentrations reported in other amidopropyl dimethylamines, and based on the data submitted, DMAPA impurities in oleamidopropyl dimethylamine can exceed the limit recommended by the Panel in the CAPB safety assessment. The Panel requested that industry provide additional information on DMAPA in oleamidopropyl dimethylamine. The Panel also noted that, for stearamidopropyl dimethylamine, the highest reported maximum use concentrations in leave-on products may yield DMAPA concentrations that exceed the limit for this impurity that the Panel recommended in the safety assessment of CAPB (e.g., greater than the EC₃ value from a LLNA on stearamidopropyl dimethylamine). The Panel did not feel that the limit is exceeded when the concentration is estimated using a QRA. Industry agreed with the Panel's request to provide a QRA for stearamidopropyl dimethylamine using the WoE NESIL of 1000 µg/cm² and the safety test data presented in this safety assessment report.

FA Amidopropyl Dimethylamines Data Profile* – June 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										
Avocamidopropyl 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
<i>January 2012</i>		
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.

Search updated April 14, 2014. No new relevant data discovered.

Fatty Acid Amidopropyl Dimethylamines – March 17-18, 2014

Belsito's Team

DR. BELSITO: -- fatty acid amidopropyl dimethylamines. So in June we issued an insufficient data announcement and asked for additional data for percutaneous absorption of cocamidopropyl dimethylamine and if it absorbed, repro toxicity, sensitization and irritation data on oleamidopropyl dimethylamine at use concentration. In September 2012 we tabled it because we were going to anticipate information from the REACH dossiers and that data was scheduled to be submitted. Anyway, the Panel -- we looked at the REACH information. We thought the REACH information would help and we were able to download -- Legal allowed us to download -- all the data from the ECHA website. So we've gotten lots of additional information on these alkyl amidopropyl dimethylamines since we said they were insufficient. But there was an issue with -- what is this under, fatty acid dimethylamines?

DR. KLAASSEN: Yes, fatty acid.

DR. BELSITO: So I thought -- if you look at page 25, it's still insufficient for a QRA on stearamidopropyl dimethylamine based upon an EC3 of 1.4 percent and an HRIPT value of 1,000 mg/cm². I think when we do that QRA, it will be more than sufficient, but we don't have that.

Also, if you look at the impurities for DMAPA in oleamidopropyl dimethylamine, it has a very high range for DMAPA in the Impurities section. And if you look at the concentration to which oleamidopropyl dimethylamine can be used, you would exceed -- if it was contaminated to that level of DMAPA, you would exceed the levels of DMAPA.

And on page 28 I just said use to 3 percent equals 300 ppm, exceeds threshold. I guess that's oleamidopropyl dimethylamine.

MS. BURNETT: I'm sorry, Dr. Belsito, are you on --

DR. BELSITO: Well, if you go to PDF page 25 --

DR. BRESLAWEK: Which section, please?

DR. SNYDER: That's the title page.

DR. BELSITO: Oh, okay, that's my general comments. So then PDF section 28.

DR. SNYDER: That's where DMAPA starts.

DR. BELSITO: It says --

DR. SNYDER: 115 ppm.

DR. BELSITO: It says "a product description sheet indicates that oleamidopropyl dimethylamine is a minimum of 88 percent pure and has a maximum concentration of 0.6 percent DMAPA." Every other product has parts per million. This says "0.6 percent DMAPA." So if that's correct, the concentration of use of oleamidopropyl dimethylamine that we're allowing in this report, which is page 28, page 46, oleamidopropyl dimethylamine is going to exceed the limits. And then for stearamidopropyl dimethylamine, again I think that it's in leave-ons of 0.02 percent. So for oleamidopropyl leave-ons, it's up to 1 percent. So if it has that level of DMAPA, it's going to exceed the limits we set on DMAPA.

I suspect that the impurities for DMAPA in oleamidopropyl dimethylamine are incorrect given the fact that their orders of magnitude are higher than what we're seeing in other of these fatty acid alkylamines, but that's an

assumption. So it would be insufficient for DMAPA contamination of oleamidopropyl dimethylamine and with the leave-ons for stearamidopropyl dimethylamine, I didn't have time to do the QRA, so with an EC3 value of 1.4 percent, I think it was 1,000 mg/cm². That should easily cover the concentration range, but I think it would be nice to do the QRA and show that it does cover it, that it is safe, because otherwise people will be saying oh, wait a minute, your EC3 was 1.4 percent and you're allowing it up to 3 percent. And anyone who doesn't understand QRA methodology and know how far you spread that, what was the concentration per centimeter squared of skin, not the concentration in the product, would think these people are -- I mean what are they doing? You're sensitizing at 1.4 and you're allowing it up to 3? But if you do the QRA on the 1,000 mg/cm², you'll see that use in those product types at 3 percent are, in fact, safe, and we need that information in the document. So we need a QRA on stearamidopropyl dimethylamine at 1,000 mg/cm² on a leave-on product to show that it is safe. And we need clarification on oleamidopropyl dimethylamine, the DMAPA contamination, because I think that's wrong and I don't know where you got it from.

DR. EISENMANN: The supplier provided it, so we'll have to go back and put -- but really the ingredients that the industry really cares about are the stearamidopropyl and behenamidopropyl, so the two larger -- if we can get those two.

DR. BELSITO: I mean that's fine and then we can always limit oleamidopropyl dimethylamine based upon the DMAPA concentration and say it should not be -- all of them are safe as used except oleamidopropyl dimethylamine, which should not be used above a certain level, and we can calculate that level based on DMAPA. But the only issue is really to do the QRA because people who don't understand QRA are going to look and say you've got an EC3 value of 1.4 percent and you're allowing it up to 3 percent.

DR. EISENMANN: Right.

DR. BELSITO: But I think when you do the QRA, you'll see that it's safe. So I don't know how to do it. At this point I think insufficient for clarification of DMAPA and oleamidopropyl dimethylamine, and for a QRA on stearamidopropyl dimethylamine based upon the EC3 value of 1.4. And that should be very easy. We can get it back at the next meeting, see the QRA clear stearamidopropyl. Behenamidopropyl is not a problem. And the oleamidopropyl, if we can't get clarification, we'll limit it. But curiously -- and my article is cited here -- in eyelid dermatitis, oleamidopropyl dimethylamine may not have a high frequency of use, but it was one of the most common sensitizers for allergic contact dermatitis of the eyelids. So maybe it is being used; maybe the DMAPA levels are too high. At the time we published that, we weren't looking at DMAPA on routine patch testing, so I wasn't privy to that information. But I have about ten years or a little more worth of data, and I could very easily run an access query on that data and see any correlation between oleamido and DMAPA sensitization.

I've been doing all the talking, folks, so say something.

DR. LIEBLER: In the discussion we talk about an additional data need for percutaneous absorption of lauramidopropyl and if it is absorbed repro in developmental. But I look at this and the lauramido has no uses, and we do have repro in developmental on the longer chain lengths and they're fine. So can we delete the lauramido?

DR. BELSITO: No, I think that the REACH data has resolved all of that as I read it. I mean we've got a lot --

DR. EISENMANN: It depends if you're comfortable reading from higher -- from a larger to a smaller, which you might not be.

DR. LIEBLER: Well, I wasn't, but it's in the report because it was raised because the small one might get absorbed more. But we get into this argument the small one might get absorbed more, so if it's absorbed and we need repro and developmental, but we really don't unless you assume that the shorter chain one would have some unique repro developmental toxicity, which I don't think is plausible.

DR. SNYDER: And the NOAELs for all the developmental studies are very high for the other ones, so that should be checked.

DR. LIEBLER: So we should try to deal with this, try to X this off of our list because I don't think it's a real issue.

DR. BELSITO: So then that just goes into the discussion that the shorter chains may have a slightly higher absorption, but we believe that we can read-across the repro toxicity for the longer chains. And even if there's slightly more absorption of the shorter chains, we're not concerned because of the high level NOAELs in the repro studies. That's just all part of discussion.

DR. LIEBLER: Okay.

DR. SNYDER: So our insufficient data announcement is still valid, but it's for a different reason now?

DR. BELSITO: Yes, the insufficient data, as far as I'm concerned, is a QRA with the EC3 of 1.4 in stearamidopropyl and clarification of the DMAPA contamination of oleamidopropyl. And if we don't get it, we'll go sufficient, but we'll restrict the concentration of use of oleamidopropyl. We'll cut it down to meet the DMAPA restrictions.

DR. LIEBLER: Fine.

DR. SNYDER: Fine.

DR. BELSITO: Okay, I think I got all of that. So save it before I lose it.

Marks' Team

DR. MARKS: In September of 2012 -- I'll mention that again, 2012, so over a year ago -- this safety assessment was tabled. They are looking for data needs including percutaneous absorption on cocamidopropyl dimethylamine and if absorbed, repro and developmental toxicity, and sensitization and the irritation data on oleamidopropyl dimethylamine at use concentration.

There was an irritation study that was received and incorporated into the report; otherwise, nothing else. So, Tom? Go ahead.

MS. BURNETT: There is a plethora of data on stearamidopropyl in the tables in the back that came from the ECHA website.

DR. MARKS: Christina, repeat that again. Which one? That was the steara, yeah, which was not in the additional data needs, so we got a lot more data. So, I guess our last didn't raise any toxicologic concerns for me, but I'll ask the Rons and Tom about that, plus any comments on the REACH data. Do we still need -- are the insufficient data needs the same, the absorption for cocamidopropyl dimethylamine? Do we still need that? Has anything changed since September 2012, other than getting more data?

So, while you're looking at that, Ron, I'll comment on the second part of it. The sensitization and irritation. We wanted the HRIPT on amidopropyl dimethylamine at 1 percent use concentration, and that was really -- the alert was there are a number of case reports of allergic contact dermatitis at 0.3 percent in the formulations. There was a new study of the oil. The problem was it was diluted 10 percent, and it was just a 24- hour patch. That's on page 20 and 49, so that really doesn't address the need for the HRIPT.

So, to me, that would be still a need -- our team had suggested -- how's this, Ron Shank -- we had suggested that it would be formulated to be non-sensitizing, using the same conclusion as CAPB, cocamidopropyl betaine. So, we were ready to move forward without the HRIPT, just as long as it was formulated to be non-sensitizing. So, that's I think where we're at with the sensitization. The new study didn't help me, other than if we have a conclusion formulated to be non-sensitizing. Ron, Ron, and Tom, what do you think about that? Do you want to go back to formulate be non-sensitizing?

DR. SHANK: Yeah, that would work. The other group (inaudible)

DR. MARKS: I know the other group. That doesn't mean we can't re-present it. Let me see. Am I going to be in tomorrow? Yes.

DR. SHANK: We wanted absorption data, I believe.

DR. MARKS: Yes.

SPEAKER: Well, we didn't get that.

DR. MARKS: And, we didn't receive it, but, now, the question is do we really need it again for us, our team. We said safe formulated to be non-sensitizing. So, is our team still on the same -- I don't have a problem with that conclusion.

DR. HILL: Well, I think my logic and my comfort level with that was based on the fact that sensitization would serve as a sentinel for any other conceivable systemic effect that might be of concern. For example, let's see, platelet -- in chronic dermal tox in rats -- I think this was the stearamido -- there was an increase in platelet values from baseline to necropsy in 25 percent, but we would be below that if you use sensitization threshold. And, similarly, in the aerosol inhalation section, I just made a comment. I think we need to be very careful how that got stated, because we have results only for a small, unlikely, not completely representative sampling of these ingredients, which, as we have drafted, we proceed to say. But, if you don't use the sensitization as a sentinel, some other concerns might pop up, because we don't have any study results on the most absorbable of this group, which is probably the lauramido, which is why they wanted penetration data. But, I think the dermal penetration data is limited. I mean, what would be preferable is a whole set of studies on laurel, but I don't think we're going to get that. So.

MR. ANSELL: Some of these are sensitizers.

DR. HILL: Yes.

MR. ANSELL: So, we're not going to develop data. What we suggest is that the stearamidopropyl dimethylamine was acceptable to the panel at the last meeting, because there HRIPT data, up to 2 percent, and we're happy with that. We're not going to go back and develop data on the lower materials which aren't used, because --

DR. HILL: Well, then, we didn't have any reported use in leave-on for lauramido, and I think that was the issue, and I think Halyna -- I seem to remember her sitting there and saying that, that -- so why study it, why would you study it if you're not using it as leave-on?

DR. MARKS: So, getting back -- this would be a tentative -- no, this would be a draft final report, safe formulated to be non-sensitizing.

MS. BURNETT: The next time you see it would be a draft final. So, it would be going out as tentative.

DR. MARKS: Yes. Since I'm the one, that's what I would move, that we issue a draft final report with a conclusion safe formulated to be non-sensitizing. Ron, Ron, and Tom?

DR. SHANK: That's okay with me.

DR. BERGFELD: You didn't want to put the top sensitization concentration at 0.2 percent. Is that right?

SPEAKER: Can we do it that way?

DR. BERGFELD: Not to exceed --

DR. MARKS: Well, I don't know what the top concentration -- there's not an HRIPT on oleamidopropyl, so I don't know what concentration is safe. It's at 1 percent use concentration, and we have case reports that elicit an allergic contact dermatitis in products containing 0.3 percent. The new study was just a 24-hour patch, so that wasn't helpful at all. So, for me, I still don't know what is the threshold level. So, that's why I would say formulate to be non-sensitizing, and that can cover everything in here, but specifically for the oleamidopropyl.

DR. HILL: Yeah. Because, I was thinking our discussion was then the options are have an HRIPT for somebody who want to use it or do a good QRA, I think.

MR. ANSELL: Well, and we would suggest that there's good data for 18 and above for the stearamido and higher and that struggling with language for non-sensitizing in the threshold of sensitization and the nestle might be overly complicated if we have a --

DR. MARKS: So, what would you propose, Jay?

MR. ANSELL: Safe as used above 18, 18 and above.

DR. MARKS: Eighteen --

MR. ANSELL: I think the stearamidopropyl dimethylamine has an HRIPT. It's clean at 2 percent. The presumption is that materials higher than that would also be okay, not go into the lower members of the group which aren't being used, because they are sensitizers, and struggling with language to how to use a sensitizer that we're not using might be overly complicated. So, we were suggesting much simpler language.

DR. MARKS: But, then what would you do? Would you eliminate those ingredients that we have in the report below this, because we have to address that.

DR. HILL: The other issue is the natural product derived. I mean, so, even though they're not in use, almondamidopropyl, avocadamidopropyl -- those are mixtures -- so how would the C18 and above apply, because you will have small amounts of C16, in some cases C12.

DR. MARKS: Jay, what I get from your suggestion is we limit the ingredients that we do in this report, if you're going to limit it to C18 and above, and that doesn't address your issue of the mixtures from these natural products, as you mentioned. Ron Shank? Tom? What do you --

DR. SHANK: I like that.

DR. MARKS: Like what?

DR. SHANK: Well, then the mixtures would have to be C18 and above, so the cocamido, which contains laurel, would have to be processed to eliminate the laurel. Is that correct?

DR. HILL: So, one way around that is to have a sort of a split conclusion that says use this or above or formulated to be non-sensitizing. We haven't done anything like that since I've been on, that I remember, but it would be very workable.

DR. MARKS: I mean, if we make a conclusion like that, we can do in the discussion dealing with C18, and, again, it would be incumbent on the manufacturer to formulate to being non-sensitizing, and they need to know within this group of ingredients which ones we're concerned about that would be in the discussion by putting C18, then we're now limiting the ingredients, and my feeling would be, then, let's go down the ingredient list and say, okay, which ones are we going to include besides stearamidopropyl dimethylamines. Yeah, that one goes across. That's clearer -- create a cross, are we going to do sunflower, are we going to do tallow, are we going to do wheat germamid? I mean, which one of these are above C18?

DR. HILL: And, then, the other catch is we also have isosteamido, so it's C18, but we don't know about the sensitization, and we have had issues occasionally with a large molecular weight iso, specifically with respect to sensitization.

MR. ANSELL: Well, perhaps the proposal for the split conclusion makes sense at this point. I think the part we want to get out of is arguing that -- requesting data that the industry's not going to provide because the industry doesn't think. They should be supported, so how we're going to handle avocado and sunflower might be addressed as you suggested.

DR. MARKS: Yeah. Basically, we leave it up to the manufacturer, that either they have data that suggests that confirms that it's a non-sensitizer. It's not being used. If they start using it, then they have to -- it should be data that support that it's non-sensitizing. So, getting back to the conclusion -- Ron, Ron, and Tom, do you -- again, going back, do you like what we had a couple years ago, or a year and a half ago, safe formulate to be non-sensitizing, and then this would be a draft final.

DR. SHANK: I like that.

DR. MARKS: Okay. Any other comments? Christina? Okay. We'll see what happens tomorrow.

Full Panel Meeting

DR. BERGFELD: So moving on then to the next ingredient, which is Dr. Marks, the fatty acid dimethylamines.

DR. MARKS: So September 2012, we tabled these ingredients, and in Christina's memo of February 21st, the needs at that point were percutaneous absorption and also if absorbed repro and developmental toxicity for the cocamidopropyl dimethylamine and sensitization and irritation on linoleamidopropyl dimethylamine.

We felt, our team, even though we may not have gotten everything as we had felt before, that we could move forward and issue a draft final report with a conclusion as safe formulate to be nonsensitizing as we did with cocamidopropyl dimethylamine, and that would take care of the sensitization issue. So I move that we issue a draft final with a conclusion safe, formulate to be nonsensitizing.

And Dr. Shank was not concerned about the repro and developmental toxicity, and obviously, we've taken care of the sensitization.

DR. BERGFELD: Any comment from the Belsito team?

DR. BELSITO: Yeah. Well, we took a slightly different tact. So we have a new EC3 on steramidopropyl dimethylamine of 1.4 percent. Now, that translated to 1,000 micrograms per centimeter squared. And we could easily calculate a QRA on that to show that it was safe. But to an observer who doesn't understand the EC3 and the way it's used, steramidopropyl dimethylamine is used in leave-ons at 2 percent, and so it would appear that we're allowing a product to go forward that's above the EC3 value. But you need to calculate micrograms per centimeter squared, and when you do that -- again, I did a very quick calculation, very quick -- and I think it will be clearly within a safe range.

The other thing that bothered me is that the range of DMAPA impurities in the oleamidopropyl dimethylamine were very high. And if you then make a calculation as to the amount of DMAPA that could be an oleamidopropyl dimethylamine, it will exceed the levels that we set. In this case we did set levels. So I think that, yeah, could we go safe as formulated to be nonsensitizing? I think we still have that question of but you have an EC3 of 1.4 and you're saying it can go to 2 percent for people who don't understand how a QRA is calculated.

But the other thing is I think that the DMAPA -- I mean, we need to go back to Industry for the DMAPA levels on all of the other oleamidopropyl dimethylamines were very low and this was reported as very high. And if, in fact, that's true, then we can go with a safe as used except oleamidopropyl dimethylamine and we have a limit for DMAPA and we can set that limit rather than saying when formulated to be nonsensitizing. That's where our group was.

So, I mean, I'm comfortable saying when formulated to be nonsensitizing, but I think that without the QRA we're subject to someone's criticism saying you had a QRA that said the EC3 -- I mean, you had a LLMA that said the EC3 was 1.4 and you're saying safe as used and there's a 2 percent use, how can you formulate that to be nonsensitizing? That's my only concern.

DR. MARKS: Could that not be handled in the discussion and clearly stated?

DR. BELSITO: Well, if we go back and calculate the QRA then we can do that and in the discussion say, "Hey, folks, if there's actually that level of DMAPA contamination in oleamidopropyl dimethylamine, it shouldn't be used at these levels. We could do that. I'm just pointing out that if we are going to go with the safe as used, I think someone still needs to run that QRA to show that 2 percent of stearamidopropyl dimethylamine is a safe use level.

DR. BERGFELD: Halyna, and then Ron.

DR. BRESLAWEK: Oh, we would be willing to do that QRA.

DR. BELSITO: Okay. So then I'm comfortable.

DR. BERGFELD: Ron.

DR. MARKS: I just want to clarify, Don, because I didn't go back to the cocamidopropyl betaine paper. I remember we had a robust discussion of trying to decide how to deal with the impurities, and I didn't -- I don't recall we actually set a level. Maybe I just don't remember.

DR. BELSITO: We set a level for DMAPA. We couldn't set a level for amidoamine.

DR. MARKS: And that's why we used formulate to be nonsensitizing.

DR. BELSITO: Right.

DR. MARKS: Because we could set a level for both impurities.

DR. BELSITO: Right. Well, we have the data for DMAPA that allowed us to settle that. We had a low alpha for amidoamine. We didn't have a no alpha so we had a problem there.

DR. MARKS: Right. So I think that's covered, as our team suggests, formulate to be nonsensitizing.

DR. BELSITO: Yeah. But I would still like to do the QRA again.

DR. MARKS: Absolutely.

DR. BELSITO: So a researcher who doesn't understand how you translate EC3 and micrograms per centimeter squared on skin which are given in that report so it's very easy to calculate the QRA and understand that we can allow it to go up to 2 percent and still be safely used.

DR. BERGFELD: Ron, did you want to comment?

DR. HILL: Right. But we had an indication that amidoamine unspecified in CAPB but that pretty much specifies it. A concentration of 0.5 percent might cause sensitization in certain finished cosmetic products. So if you don't assume that the sensitization is strictly coming from DMAPA, and I don't, then we have ingredients where we have mixtures which we really don't know what the concentrations of the various fatty acids derivatizing that dimethylamine amino fragment are. And so that was really the logic, I think, behind using the formulated to be nonsensitizing.

But isn't this the one where we talked about the split conclusion where we said -- I don't remember if it was this one. It was a different one? Okay, never mind. But I think that was the logic of the nonsensitizing, was that it allowed for whatever the fatty acid component is if we don't know.

DR. BELSITO: I have no problems with the addition of the formula being nonsensitizing. That's not the issue. It's just that there's data there that we could do some more calculations with and haven't, and also there's data there on the oleamidopropyl dimethylamine that it just doesn't make sense in terms of DMAPA contamination when you look at the levels that we're told are in other oleamidopropyl dimethylamines. And I would just like that clarified. So I'm comfortable with your conclusion -- do the QRA and, you know, we'll clarify the DMAPA levels.

DR. BERGFELD: So we're going to do that in the discussion?

DR. BELSITO: Yes.

DR. BERGFELD: Yes?

DR. BELSITO: And so we can move.

DR. BERGFELD: Can we move?

DR. MARKS: We can move forward with a draft final and those will be included in draft final. We'll have another look at it as well as the public.

DR. BERGFELD: So you're seconding it?

DR. MARKS: Yes.

DR. BERGFELD: Is there any other discussion? Dan? Paul? Curt? None? All right. I'll move the question. All those in favor indicate by raising your hands. Thank you. Unanimous.

(Motion passed)

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, Senior Scientific Analyst/Writer; Ivan Boyer, Ph.D., Toxicologist CIR; and Bart Heldreth, Ph.D., Chemist CIR.

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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 relevant animal and human data reviewed for these ingredients indicate that they are potential dermal sensitizers. The Panel concluded that fatty acid amidopropyl dimethylamines were safe as cosmetic ingredients when they are formulated to be non-sensitizing.

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 when they are formulated to be non-sensitizing, which may be based on a quantitative risk assessment.” The Panel was aware of impurities that may exist in the amidopropyl betaines and expressed concern over 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) of 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 along with a summary of the QRA on these 2 chemicals 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 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 differ only 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.

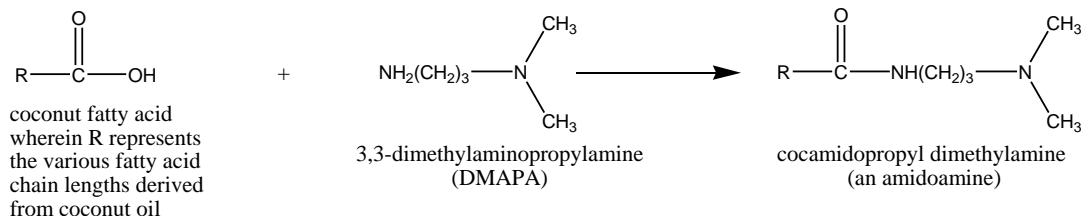


Figure 1. Synthesis of Cocamidopropyl Dimethylamine

Despite the long alkyl chain substituents therein, these ingredients are readily solubilized in water, as they are easily converted to ammonium salts (i.e., cationic surfactants) at even mildly acidic pH values (i.e., the tertiary amines are protonated to form ammonium cations; these ingredients are alkaline materials with pK_b values in the range of 5-6).^{4,5} Because of their high polarity, both as the free tertiary amines and as the ammonium salts formed in-situ, these ingredients are excellent dissipators of 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 °C and < 175 °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 NO₂ 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, < 1 ppm 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 a hair and skin conditioning agent. 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 is used in cosmetic sprays, including hair tonics and dressings. Oleamidopropyl dimethylamine and stearamidopropyl dimethylamine may also be used in colognes and indoor tanning products – use in this fashion cannot be confirmed. When used in cosmetic sprays, these ingredients could possibly be inhaled. The maximum concentration of these ingredients reported to be used in a spray product is 0.15% (oleamidopropyl dimethylamine) in a hair tonic, dressing or other hair grooming pump spray product. 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 currently 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.² The maximum dermal absorption rate was calculated to be 2.40×10^{-6} mg/cm²/h. The calculations were based on an instantaneous deposition dose of 9257 mg and a skin area of 2000 cm².

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 LD₅₀ 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 (organs not described) 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 LD₅₀ 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 CrI:WI(Han) rats/sex/dose via gavage at doses 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 abnormalities 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 those in control animals.

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 with 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 mesenteric 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. (Full details on which organs were examined microscopically were not provided in the ECHA summary.) 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 with OECD Guideline 411 in groups of 5 male and 5 female New Zealand White rabbits.² Test solutions were prepared fresh weekly in 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, and 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. The animals

were collared to prevent oral ingestion of the test material. 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 with 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 pre-mating period for males, and during the first week of the pre-mating 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 pre-coital 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 collared to prevent oral ingestion of the test material. 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. Reproductive organs that were examined included the prostate, seminal vesicles, testis, epididymis in males and the ovaries, uterus, and vagina in females. 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 weights 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 $p \leq 0.01$) from Day 15 through Day 21 of gestation.

Slightly impaired implantation was observed, along with slightly decreased litter sizes, 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, the maternal NOAEL was determined to be 100 mg/kg body weight/day based on variations in body weight and food-consumption data, and the developmental NOAEL was determined to be 200 mg/kg body weight/day in this study.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 ≥ 50 µg/plate in *S. typhimurium* and ≥ 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 experiment 1 of this 2-part study, the test material was tested up to 10 µg/ml, without and with S9 metabolic activation. In experiment 2, the test material was tested up to 25 and 10 µg/ml, without and with S9, respectively. Incubation for cells in the first experiment was 3 h, and in the second experiment, incubation was 3 h and 24 h or 48 h. In both experiments, no statistically or biologically significant increased numbers 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.^{2,33-38} 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.

Dermal irritation studies are summarized in Table 5.^{2,39-42} Stearamidopropyl dimethylamine was considered not irritating in non-human studies when tested at 100%. Behenamidopropyl dimethylamine (up to 3%), 0.1% oleamidopropyl dimethylamine, and 0.045% stearamidopropyl dimethylamine in personal care products were not irritating in several in-use studies.

Dermal sensitization studies are summarized in Table 6.⁴³⁻⁵⁷ Behenamidopropyl dimethylamine at 0.3% diluted to 1%, 4% brassicamidopropyl dimethylamine, and stearamidopropyl dimethylamine up to 2% in hair conditioners were not contact sensitizers. However, irritation reactions were observed.

CLINICAL 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.^{58,59} Reactions were especially prevalent when the baby lotion was 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 oleamidopropyl 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 of 12 tested, 75%), and myristamidopropyl dimethylamine (6 patients, 46%). Five patients reacted to isostearamidopropyl dimethylamine, minkamidopropyl dimethylamine, and cocamidopropyl dimethylamine (12 patients tested). The remaining substances elicited a 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 3 cases of allergic contact dermatitis in patients that had used a body lotion.⁶⁰ 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 noted for hydroxycitronellal and quaternium-15. Further tests showed a positive reaction to oleamidopropyl dimethylamine. The itching improved after the patient discontinued using the body lotion.⁶⁰

Oleamidopropyl Dimethylamine and Cocamidopropyl Dimethylamine

A 10-year retrospective study of patients with allergic eyelid dermatitis investigated the possible allergens.⁶¹ Patch testing was performed in these patients with the NACDG's standard screening tray and other likely allergen trays. 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 cocamidopropyl betaine (CAPB) have been summarized in Table 7 and Table 8, respectively.¹ In the tables, amidoamine refers to cocamidopropyl dimethylamine.

QUANTITATIVE RISK ASSESSMENT

DMAPA and Cocamidopropyl Dimethylamine ("Amidoamine") in CAPB

The Council's Task Force on Sensitization Risk from CAPB Impurities (Task Force) conducted a quantitative risk assessment (QRA) of DMAPA and cocamidopropyl dimethylamine ("amidoamine") in support of the CIR safety assessment of CAPB.^{1,62-64} Both of these substances are reactants used in the synthesis of CAPB and are, thus, present as impurities in CAPB used as ingredients in cosmetic formulations. DMAPA is present in CAPB ingredients, as supplied ("raw"; typically 30% CAPB) to cosmetics manufacturers at 0.00025% to 0.01%, and "amidoamine" is present at 0.05% to 5.0% (0.5% was "typical" and 1.5% was the suggested maximum concentration). The Task Force derived conservative weight-of-evidence no expected sensitization induction levels (WoE NESILs) of 425 µg/cm² for DMAPA, based on data from 8 LLNAs performed with a variety of vehicles, and 180 µg/cm² for "amidoamine," based on data from a HRIPT and a LLNA. The NESILs were then used to calculate margins of safety (MOSs) for the potential for sensitization from dermal exposure to these impurities in cosmetic ingredients, assuming 0.01% DMAPA and 0.5% "amidoamine" in "raw" CAPB and default safety assessment factors (SAFs). CAPB ingredients, as supplied, are used at concentrations up to 11% in cosmetic products.¹ The MOSs calculated for DMAPA were acceptable for all 35 product categories addressed in the QRA, and for "amidoamine" were acceptable for 30 of the 35 categories.⁶² The Task Force recommended refining the QRA for "amidoamine" in the remaining 5 product categories, and that "raw" CAPB users should set the CAPB concentrations in finished products based on QRAs for these impurities.

Stearamidopropyl Dimethylamine

The Council's CIR Science and Support Committee (SSC) performed a QRA of potential dermal sensitization for stearamidopropyl dimethylamine, in accordance with the procedure described above for DMAPA and "amidoamine" in CAPB.^{1,65} The CIR SSC derived a conservative WoE NESIL of 1000 µg/cm², based on data from 11 HRIPTs, a guinea pig maximization test, a Buehler guinea pig test and a LLNA. Greater weight was given to the HRIPT data than the animal data, and the 1000 µg/cm² NESIL reflects the highest concentration tested in the HRIPTs. The MOSs calculated for stearamidopropyl dimethylamine were acceptable for 9 of the 22 product categories addressed, assuming the highest maximum use concentration reported for each category.⁶² This includes use at 5% in hair conditioners, for example. The CIR SSC concluded that further justification is needed for current use levels of this ingredient in the remaining 13 product categories.

SUMMARY

The fatty acid amidopropyl dimethylamines, referred to as "amidoamines" function primarily as antistatic agents in cosmetic products. The CIR Expert Panel has expressed 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/cm²/h.

The LD₅₀ 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, the maternal NOAEL was determined to be 100 mg/kg body weight/day based on variations in body weight and food consumption data, and the developmental NOAEL was determined to be 200 mg/kg body weight/day 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.

Quantitative risk assessments of these ingredients may be performed to ensure acceptable levels of risk in consumers.

DISCUSSION

The CIR Expert Panel had expressed concern in the previous Cocamidopropyl Betaine and Related Fatty Acid Amidopropyl Betaines (CAPB) safety assessment about the impurities that have sensitizing potential. These impurities of CAPB include the ingredients discussed in this safety assessment. The Panel especially recognizes that there are increasing concerns about the contact sensitization potential of oleamidopropyl dimethylamine, which was recently added to the North American Contact Dermatitis Group's test panel. The CIR Expert Panel noted that, although a safe conclusion was reached for this ingredient group, DMAPA in oleamidopropyl dimethylamine appeared to be present at concentrations greater than those reported for other amidopropyl dimethylamines. Based on the data submitted, DMAPA in oleamidopropyl dimethylamine could exceed the limit recommended by the Panel in the CAPB safety assessment (i.e., 0.01% DMAPA in "raw" CAPB used at the highest reported maximum use concentration of 11% in the product category "other shaving preparations"). The Panel requested that industry provide additional information on DMAPA in oleamidopropyl dimethylamine.

The Panel also noted that, for stearamidopropyl dimethylamine, the highest reported maximum use concentration in leave-on products may result in DMAPA concentrations that exceed the limit for this impurity recommended by the Panel recommended for CAPB. Eleven HRIPT studies of normal human subjects indicated that no sensitization was induced by stearamidopropyl dimethylamine applied to the skin at concentrations of use; 2 rodent sensitization studies were also negative. However, a LLNA yielded an EC₃ of 1.4% (350 µg/cm²), indicating that stearamidopropyl dimethylamine is a potential sensitizer. A QRA based on the HRIPTs and rodent studies yielded a conservative, WoE NESIL of 1000 µg/cm² for stearamidopropyl dimethylamine, and confirmed that this ingredient has the potential to cause sensitization at reported use concentrations in many categories of finished cosmetic products. The Panel concluded that non-sensitizing concentrations of fatty acid amidopropyl dimethylamine ingredients in finished products should be determined by the formulators based on QRAs for these ingredients with fatty acid groups below C18 and for DMAPA, using appropriate NESILs for these substances. The Panel advises industry to continue minimizing the concentrations of the sensitizing impurity DMAPA.

The Panel expressed concern about the potential ability of amidopropyl dimethylamines with shorter fatty acids to be absorbed through the skin and into the systemic circulation. However, the high NOAELs in reproductive toxicity tests of amidopropyl dimethylamines with longer fatty acids alleviated this concern. The Panel felt that the overall toxicological data supported the safety of amidopropyl dimethylamines with fatty acid chain lengths C18 or higher.

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 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 0.15% 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>.

CONCLUSION

The CIR Expert Panel concluded that the 24 fatty acid amidopropyl dimethylamines ingredients listed below are safe in cosmetics when they are formulated to be non-sensitizing.

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

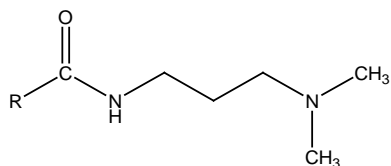
Ingredient & CAS No.	Definition
<u>Almondamidopropyl Dimethylamine</u>	Almondamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR), where RCO- represents the fatty acids derived from almond oil. <i>This amidoamine results from the reaction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

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
<u>Palmitamidopropyl Dimethylamine</u> 39669-97-1 [872428-99-4]	Palmitamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). <i>This amidoamine results from the reaction of DMAPA and palmitic acid.</i>
<u>Ricinoleamidopropyl Dimethylamine</u> 20457-75-4	Ricinoleamidopropyl Dimethylamine is the amidoamine that conforms generally to the structure shown in Figure 2 (redrawn by CIR). <i>This amidoamine results from the reaction of DMAPA and ricinoleic acid.</i>
<u>Sesamidopropyl Dimethylamine</u>	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. <i>This amidoamine results from the reaction of DMAPA and the fatty acids derived from sesame oil.</i>
<u>Soyamidopropyl Dimethylamine</u> 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. <i>This amidoamine results from the reaction of DMAPA and the fatty acids derived from soy.</i>
<u>Stearamidopropyl Dimethylamine</u> 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). <i>This amidoamine results from the reaction of DMAPA and stearic acid.</i>
<u>Sunflowerseedamidopropyl Dimethylamine</u>	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. <i>This amidoamine results from the reaction of DMAPA and the fatty acids derived from sunflower seed oil.</i>
<u>Tallamidopropyl Dimethylamine</u> 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. <i>This amidoamine results from the reaction of DMAPA and the fatty acids derived from tall oil.</i>
<u>Tallowamidopropyl Dimethylamine</u> 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. <i>This amidoamine results from the reaction of DMAPA and the fatty acids derived from tallow.</i>
<u>Wheat Germamidopropyl Dimethylamine</u>	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. <i>This amidoamine results from the reaction of DMAPA and the fatty acids derived from wheat germ oil.</i>

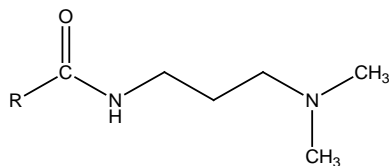
Figure 2. Structures

1. Almondamidopropyl Dimethylamine



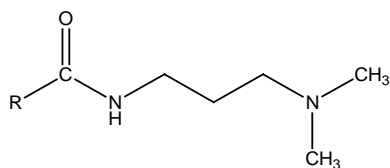
wherein RC(O) represents any of the fatty acid residues derived from almond oil

2. Avocadamidopropyl Dimethylamine



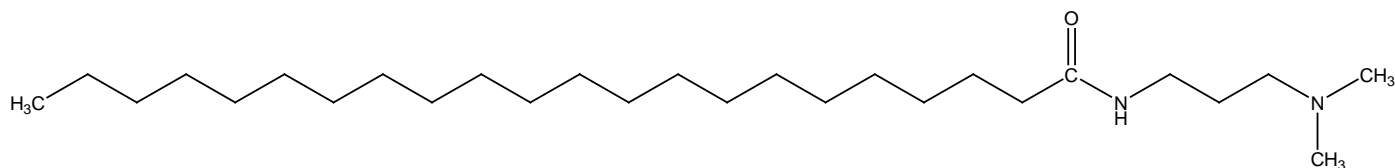
wherein RC(O) represents any of the fatty acid residues derived from Persea Gratissima (Avocado) Oil

3. Babassuamidopropyl Dimethylamine

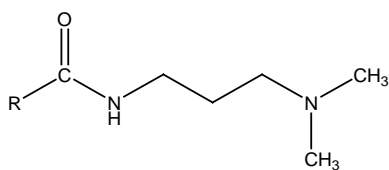


wherein RC(O) represents any of the fatty acid residues derived from Orbignya oleifera (babassu) oil

4. Behenamidopropyl Dimethylamine

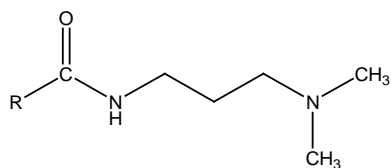


5. Brassicamidopropyl Dimethylamine



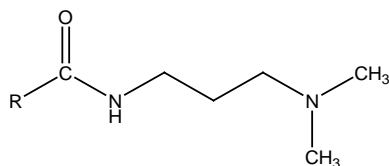
wherein RC(O) represents any of the fatty acid residues from Brassica Campestris (Rapeseed) Seed Oil

6. Cocamidopropyl Dimethylamine



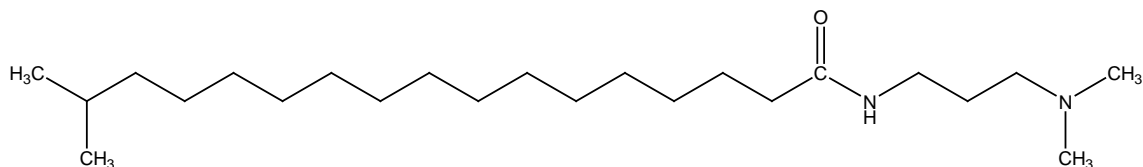
wherein RC(O) represents any of the fatty acid residues derived from coconut oil

7. **Dilinoleamidopropyl Dimethylamine**

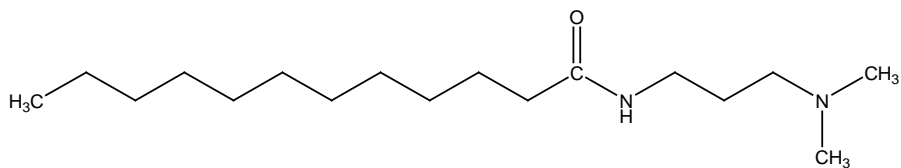


wherein RC(O) represents the variety of 36-carbon dicarboxylic acid residues, formed by the catalytic dimerization of linoleic acid

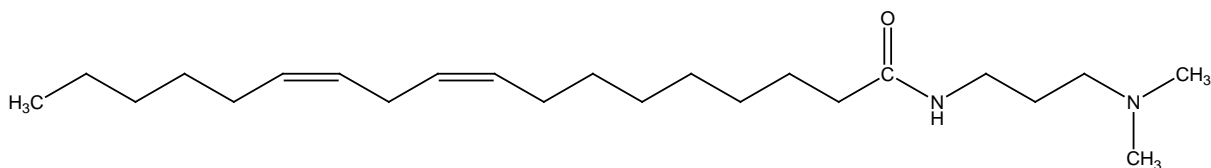
8. **Isostearamidopropyl Dimethylamine** (one example of an “iso”)



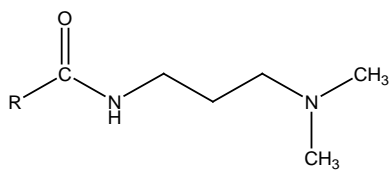
9. **Lauramidopropyl Dimethylamine**



10. **Linoleamidopropyl Dimethylamine**

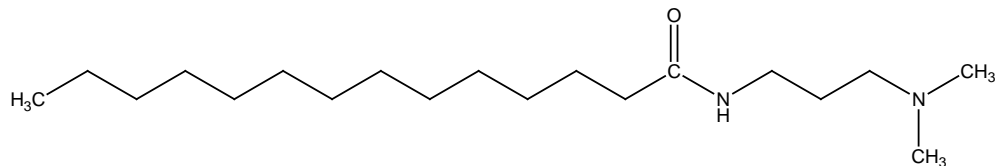


11. **Minkamidopropyl Dimethylamine**

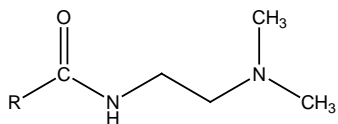


wherein RC(O) represents any of the fatty acid residues derived from mink oil

12. **Myristamidopropyl Dimethylamine**

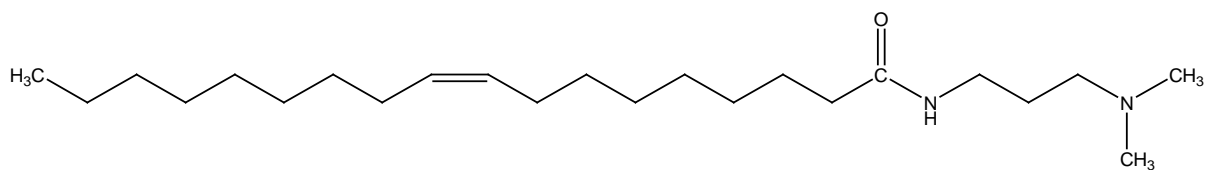


13. **Oatamidopropyl Dimethylamine**

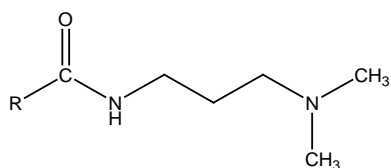


wherein RC(O) represents any of the fatty acid residues derived from Avena Sativa (Oat) Kernel Oil

14. **Oleamidopropyl Dimethylamine**

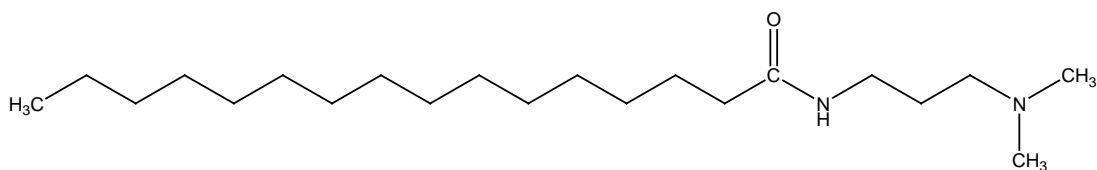


15. **Olivamidopropyl Dimethylamine**

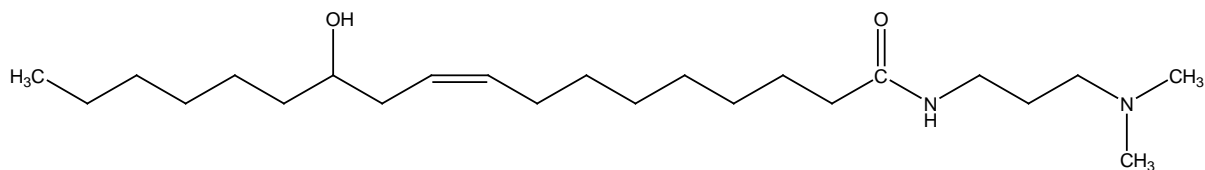


wherein RC(O) represents any of the fatty acid residues derived from olive oil

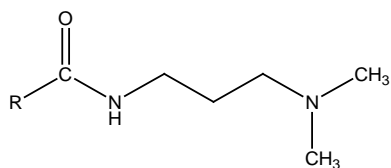
16. **Palmitamidopropyl Dimethylamine**



17. **Ricinoleamidopropyl Dimethylamine**

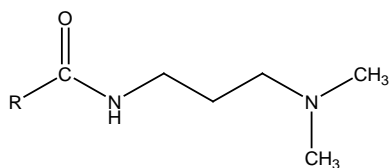


18. **Sesamidopropyl Dimethylamine**



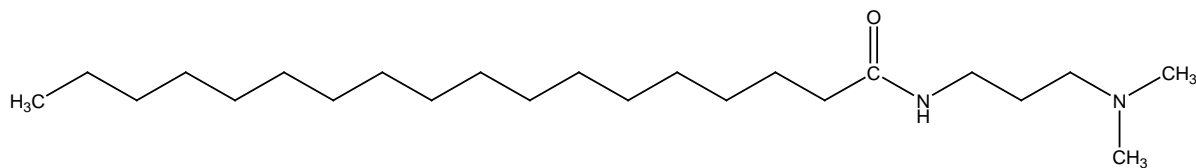
wherein RC(O) represents any of the fatty acid residues derived from sesame oil

19. **Soyamidopropyl Dimethylamine**

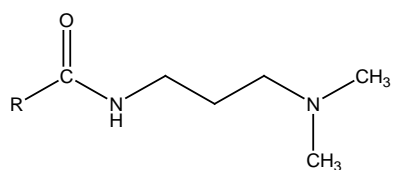


wherein RC(O) represents any of the fatty acid residues derived from soy

20. **Stearamidopropyl Dimethylamine**

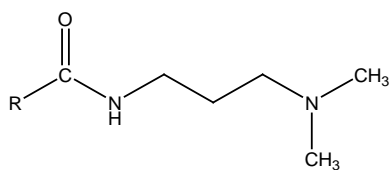


21. **Sunflowerseedamidopropyl Dimethylamine**



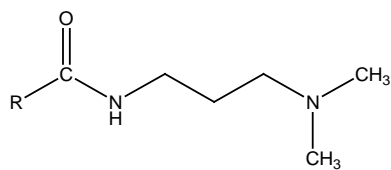
wherein RC(O) represents any of the fatty acid residues derived from sunflower seed oil

22. **Tallamidopropyl Dimethylamine**



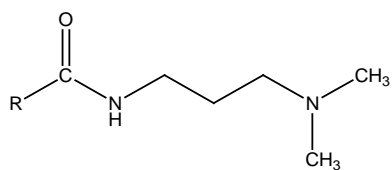
wherein RC(O) represents any of the fatty acid residues derived from tall oil

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
<i>Behenamidopropyl Dimethylamine</i>		
Molecular Weight g/mol	424.75	⁶⁶
Molecular Volume cm ³ /mol @ 20 °C	487.4	⁶⁶
Density/Specific Gravity g/cm ³ @ 20 °C	0.871	⁶⁶
Vapor pressure mmHg@ 25 °C	6.30 x 10 ⁻¹²	⁶⁶
Boiling Point °C	544.8	⁶⁶
log P @ 25 °C	9.656	⁶⁶
<i>Cocamidopropyl Dimethylamine</i>		
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
<i>Lauramidopropyl Dimethylamine</i>		
Molecular Weight g/mol	284.48	⁶⁶
Molecular Volume cm ³ /mol @ 20 °C	322.3	⁶⁶
Density/Specific Gravity g/cm ³ @ 20 °C	0.882	⁶⁶
Vapor pressure mmHg@ 25 °C	3.17 x 10 ⁻⁷	⁶⁶
Boiling Point °C	418.9	⁶⁶
Melting Point °C	28.5-30.0	⁵
log P @ 25 °C	4.561	⁶⁶

Table 2. Physical and chemical properties.

Property	Value	Reference
<i>Linoleamidopropyl Dimethylamine</i>		
Molecular Weight g/mol	364.61	⁶⁶
Molecular Volume cm ³ /mol @ 20 °C	408.6	⁶⁶
Density/Specific Gravity g/cm ³ @ 20 °C	0.892	⁶⁶
Vapor pressure mmHg@ 25 °C	2.69 x 10 ⁻¹⁰	⁶⁶
Boiling Point °C	504.3	⁶⁶
log P @ 25 °C	6.805	⁶⁶
<i>Myristamidopropyl Dimethylamine</i>		
Molecular Weight g/mol	312.53	⁶⁶
Molecular Volume cm ³ /mol @ 20 °C	355.3	⁶⁶
Density/Specific Gravity g/cm ³ @ 20 °C	0.879	⁶⁶
Vapor pressure mmHg@ 25 °C	3.84 x 10 ⁻⁸	⁶⁶
Boiling Point °C	445.8	⁶⁶
log P @ 25 °C	5.580	⁶⁶
<i>Oleamidopropyl Dimethylamine</i>		
Physical Form	Liquid	¹¹
Color	Amber	¹¹
Molecular Weight g/mol	366.62	⁶⁶
Molecular Volume cm ³ /mol @ 20 °C	414.9	⁶⁶
Density/Specific Gravity g/cm ³ @ 20 °C	0.883	⁶⁶
Vapor pressure mmHg@ 25 °C	2.57 x 10 ⁻¹⁰	⁶⁶
Boiling Point °C	504.8	⁶⁶
Solubility	Slightly in water, readily when neutralized with acid	¹¹
log P @ 25 °C	7.209	⁶⁶
pH @ 25 °C	9.0-10.0	¹¹

Table 2. Physical and chemical properties.

Property	Value	Reference
<i>Palmitamidopropyl Dimethylamine</i>		
Molecular Weight g/mol	340.59	⁶⁶
Molecular Volume cm ³ /mol @ 20 °C	388.3	⁶⁶
Density/Specific Gravity g/cm ³ @ 20 °C	0.876	⁶⁶
Vapor pressure mmHg@ 25 °C	4.52 x 10 ⁻⁹	⁶⁶
Boiling Point °C	471.8	⁶⁶
log P @ 25 °C	6.599	⁶⁶
<i>Ricinoleamidopropyl Dimethylamine</i>		
Molecular Weight g/mol	382.62	⁶⁶
Molecular Volume cm ³ /mol @ 20 °C	412.8	⁶⁶
Density/Specific Gravity g/cm ³ @ 20 °C	0.926	⁶⁶
Vapor pressure mmHg@ 25 °C	8.20 x 10 ⁻¹⁴	⁶⁶
Boiling Point °C	537.9	⁶⁶
log P @ 25 °C	5.395	⁶⁶
<i>Stearamidopropyl Dimethylamine</i>		
Physical Form	Waxy flake	¹³
Molecular Weight g/mol	368.64	⁶⁶
Molecular Volume cm ³ /mol @ 20 °C	421.7	⁶⁶
Density/Specific Gravity g/cm ³ @ 20 °C	0.874	⁶⁶
Vapor pressure mmHg@ 25 °C	5.19 x 10 ⁻¹⁰ -	⁶⁶
	9.03 x 10 ⁻¹⁰	
Boiling Point °C	490.6 - 496.9	⁶⁶
Melting Point °C	58.5-59.5; 65-70	^{5,13}
log P @ 25 °C	7.618 - 7.629	⁶⁶

Table 3a. Frequency (2014) and concentration of use (2012) according to duration and type of exposure for fatty acid amidopropyl dimethylamine ingredients.^{17,18}

	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>
	Behenamidopropyl Dimethylamine		Brassicamidopropyl Dimethylamine		Cocamidopropyl Dimethylamine		Isostearamidopropyl Dimethylamine	
Totals¹	53	0.3-3	5	0.2-4	17	0.003-6.5	10	0.04-0.38
<i>Duration of Use</i>								
Leave-On	2	1	NR	0.2	6	0.03	1	0.04
Rinse Off	51	0.3-3	5	4	11	0.003-6.5	9	0.38
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
<i>Exposure Type</i>								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray? ^{2,6}	NR	1	NR	NR	5	NR	1	NR
Reported Spray ³	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder? ^{4,6}	NR	NR	NR	NR	5	NR	1	NR
Reported Powder ⁵	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	5	NR	NR	0.2	15	0.03-6.5	1	0.04
Deodorant (underarm)-Spray? ²	NR	NR	NR	NR	NR	NR	NR	NR
Reported Spray ³	NR	NR	NR	NR	NR	NR	NR	NR
Reported as Not Spray ³	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	48	0.3-3	5	4	2	0.003	9	0.38
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	5	NR	NR	NR	5	1.3-5	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Laureamidopropyl Dimethylamine		Minkamidopropyl Dimethylamine		Oleamidopropyl Dimethylamine		Palmitamidopropyl Dimethylamine	
Totals¹	2	NR	1	NR	13	0.0015-1	1	NR
<i>Duration of Use</i>								
Leave-On	NR	NR	NR	NR	4	0.0015-1	NR	NR
Rinse Off	2	NR	1	NR	9	0.8	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
<i>Exposure Type</i>								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray? ^{2,6}	NR	NR	NR	NR	4	0.0015-1	NR	NR
Reported Spray ³	NR	NR	NR	NR	NR	0.15 ^a	NR	NR
Incidental Inhalation-Powder? ^{4,6}	NR	NR	NR	NR	NR	1	NR	NR
Reported Powder ⁵	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	NR	NR	NR	1	NR	NR
Deodorant (underarm)-Spray? ²	NR	NR	NR	NR	NR	NR	NR	NR
Reported Spray ³	NR	NR	NR	NR	NR	NR	NR	NR
Reported as Not Spray ³	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	1	NR	13	0.0015-0.8	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 3a. Frequency (2014) and concentration of use (2012) according to duration and type of exposure for fatty acid amidopropyl dimethylamine ingredients.^{17,18}

	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>
Totals¹	551	0.01-5						
<i>Duration of Use</i>								
Leave-On	84	0.02-3						
Rinse Off	467	0.01-5						
Diluted for (Bath) Use	NR	NR						
<i>Exposure Type</i>								
Eye Area	NR	1.5-1.8						
Incidental Ingestion	NR	1.7						
Incidental Inhalation-Spray? ^{2, 6}	64	1.8-3						
Reported Spray ³	NR	NR						
Incidental Inhalation-Powder? ^{4,6}	20	NR						
Reported Powder ⁵	NR	1.7						
Dermal Contact	26	0.01-2						
Deodorant (underarm)-Spray? ²	NR	NR						
Reported Spray ³	NR	NR						
Reported as Not Spray ³	NR	NR						
Hair - Non-Coloring	431	0.05-5						
Hair-Coloring	94	0.3-2						
Nail	NR	NR						
Mucous Membrane	NR	1.7-1.8						
Baby Products	1	NR						

NR = Not reported.

1. Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
2. It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
3. Use in a spray product has been reported in response to a survey conducted by the Council.
4. It is possible these products may be powders, but it is not specified whether the reported uses are powders.
5. Use in a powder product has been reported in response to a survey conducted by the Council.
6. Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
 - a. 0.15% in a hair tonic, dressing, or other hair grooming aid pump spray.

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
<i>In Vitro</i>				
Behenamidopropyl Dimethylamine	0.3% in a shampoo, diluted with deionized water to a 10% solution	EpiOcular irritation study	No/minimal irritation	33,36
Behenamidopropyl Dimethylamine	0.3% in a shampoo, diluted with deionized water to a 10% solution	EpiOcular irritation study	No/minimal irritation	34,36
Stearamidopropyl Dimethylamine	0.045% in a pre-shave scrub, diluted to 10% solution	EpiOcular irritation study	No/minimal irritation	37
Stearamidopropyl Dimethylamine	2% in a hair conditioner, diluted to 10% solution	EpiOcular irritation study	No/minimal irritation	35
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 ≥ 55.1); not severely irritating/not corrosive	2
<i>In Vivo</i>				
Dilinooleamidopropyl Dimethylamine	In a 2% dilution with corn oil	Eye irritation study in a single male rabbit (strain not described)	No irritation	38
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
<i>Non-Human</i>				
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
<i>Human</i>				
Behenamidopropyl Dimethylamine	3% in a hair conditioner	Two week daily use study in 28 female subjects	No dermal irritation or other adverse events	³⁹
Behenamidopropyl Dimethylamine	0.3% in a shampoo	Two week daily use study in 28 female subjects	No dermal irritation or other adverse events	⁴⁰
Oleamidopropyl Dimethylamine	0.1% 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	⁴²
Stearamidopropyl Dimethylamine	0.045% in a pre-shave scrub	Two week daily use study in 30 male subjects	No dermal irritation	⁴¹

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	44
Stearamidopropyl Dimethylamine	NA	QSAR modeling for sensitization using TOPKAT	Not sensitizing – no compounds sufficiently similar to the query structure were found	43
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	47
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	46
Brassicamidopropyl Dimethylamine	4% in a hair masque, tested neat	HRIPT; semi-occlusive with 0.2 ml sample; 102 subjects completed	No skin reactivity observed	49
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	50
Stearamidopropyl Dimethylamine	0.045% in a body lotion	HRIPT; occlusive with 0.2ml sample; 102 subjects completed	No adverse events	45
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	51
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	48
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	52
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	53
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	54
Stearamidopropyl Dimethylamine	2% in a hair conditioner	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	45
Stearamidopropyl Dimethylamine	diluted with distilled water to 0.6% in a hair conditioner	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	55
Stearamidopropyl Dimethylamine	diluted with distilled water to 0.6% in a hair conditioner	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 1 or 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	56
Stearamidopropyl Dimethylamine	diluted with distilled water to 0.6% in a hair conditioner	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	57

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
<i>Sensitization Studies – Non-Human</i>				
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 = $6.1 \times 10^2 \mu\text{g}/\text{cm}^2$]; 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 = $1.5 \times 10^2 \mu\text{g}/\text{cm}^2$].	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.	67
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 exposures at a dose volume of 0.4 ml [estimated dose/unit area = $2.5 \times 10^4 \mu\text{g}/\text{cm}^2$]; 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.	68
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 ≥ 0.5 at 24 h after the removal of the patch. After 48 h, 6 animals had a reaction score ≥ 0.5 . Three out of 10 animals had a reaction score of 2. At the second challenge, 7 guinea pigs had a score ≥ 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 ≥ 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.	69
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 ≥ 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 ≥ 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.	69

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).	⁷⁰
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.	^{71,72}
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.	⁷³
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.	⁷⁴
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 x 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.	⁷⁵

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).	⁷⁶
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).	⁷⁷
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).	⁷⁸

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).	⁷⁹
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.	⁸⁰
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).	⁸¹
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).	⁸²

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).	⁸³
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).	⁸⁴
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).	⁸⁵
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).	⁸⁶

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).	⁸⁷
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).	⁸⁸
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).	⁸⁹

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.	^{89,90}
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).	⁹¹

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	<p>-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.</p> <p>-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.</p>	⁹²
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.	⁹³
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.	⁹⁴
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.	⁹⁵
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).	⁹⁶
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.	⁹⁷

Table 9. Quantitative risk assessment of stearamidopropyl dimethylamine in cosmetic products.

Product Category	Max Use Concentration(%)	Product Exposure (µg/cm ²)	CEL (µg/cm ²)	NESIL (µg/cm ²)	SAF	AEL	AEL/CEL
Eye lotion	1.8	2170	39.06	1000.00	300.00	3.33	0.09
Eye makeup remover	1.5	900	13.50	1000.00	100.00	10.00	0.74
Cologne and toilet waters	1.8	17700	318.60	1000.00	100.00	10.00	0.03
Hair conditioners	5	200	10.00	1000.00	100.00	10.00	1.00
Rinses (noncoloring)	1	170	1.70	1000.00	100.00	10.00	5.88
Shampoos (noncoloring)	2	170	3.40	1000.00	30.00	33.33	9.80
Tonics, dressings and other hair grooming aids	3	990	29.70	1000.00	100.00	10.00	0.34
Other hair preparations (non-coloring) rinse-off	0.5	200	1.00	1000.00	100.00	10.00	10.00
*Hair dyes and colors	2	1000	20.00	1000.00	100.00	10.00	0.50
Face powders	1.7	1000	17.00	1000.00	100.00	10.00	0.59
Foundations	0.25	3170	7.93	1000.00	100.00	10.00	1.26
Lipsticks	1.7	11460	194.82	1000.00	300.00	3.33	0.02
Makeup bases	1.6	4200	67.20	1000.00	100.00	10.00	0.15
Bath soaps and detergents	1.8	10	0.18	1000.00	100.00	10.00	55.56
Aftershave lotions	2	2210	44.20	1000.00	100.00	10.00	0.23
Preshave lotions (all types)	0.05	2200	1.10	1000.00	100.00	10.00	9.09
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.07	900	0.63	1000.00	100.00	10.00	15.87
Face and neck creams, lotions, powders	1.2	2700	32.40	1000.00	100.00	10.00	0.31
Body and hand creams, lotions and powders	1.5	1120	16.80	1000.00	300.00	3.33	0.20
Moisturizers	1	2700	27.00	1000.00	100.00	10.00	0.37
Other skin care products	0.1	2200	2.20	1000.00	100.00	10.00	4.55
Indoor tanning preparations	2	2200	44.00	1000.00	100.00	10.00	0.23

Shaded rows indicate the ratio of AEL x CEL⁻¹ is less than 1.

*Note that this product category may be diluted prior to application.

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2014 FDA RAW VCRP DATA

05A - Hair Conditioner	BEHENAMIDOPROPYL DIMETHYLAMINE	45
05F - Shampoos (non-coloring)	BEHENAMIDOPROPYL DIMETHYLAMINE	1
05I - Other Hair Preparations	BEHENAMIDOPROPYL DIMETHYLAMINE	2
10A - Bath Soaps and Detergents	BEHENAMIDOPROPYL DIMETHYLAMINE	5
05A - Hair Conditioner	BRASSICAMIDOPROPYL DIMETHYLAMINE	5
05F - Shampoos (non-coloring)	COCAMIDOPROPYL DIMETHYLAMINE	2
10A - Bath Soaps and Detergents	COCAMIDOPROPYL DIMETHYLAMINE	5
12A - Cleansing	COCAMIDOPROPYL DIMETHYLAMINE	4
12C - Face and Neck (exc shave)	COCAMIDOPROPYL DIMETHYLAMINE	2
12F - Moisturizing	COCAMIDOPROPYL DIMETHYLAMINE	2
12G - Night	COCAMIDOPROPYL DIMETHYLAMINE	1
12J - Other Skin Care Preps	COCAMIDOPROPYL DIMETHYLAMINE	1
05A - Hair Conditioner	ISOSTEARAMIDOPROPYL DIMETHYLAMINE	9
12D - Body and Hand (exc shave)	ISOSTEARAMIDOPROPYL DIMETHYLAMINE	1
05D - Permanent Waves	LAURAMIDOPROPYL DIMETHYLAMINE	1
10A - Bath Soaps and Detergents	LAURAMIDOPROPYL DIMETHYLAMINE	1
05A - Hair Conditioner	MINKAMIDOPROPYL DIMETHYLAMINE	1
05A - Hair Conditioner	OLEAMIDOPROPYL DIMETHYLAMINE	8
05F - Shampoos (non-coloring)	OLEAMIDOPROPYL DIMETHYLAMINE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	OLEAMIDOPROPYL DIMETHYLAMINE	4
05A - Hair Conditioner	PALMITAMIDOPROPYL DIMETHYLAMINE	1
01C - Other Baby Products	STEARAMIDOPROPYL DIMETHYLAMINE	1
05A - Hair Conditioner	STEARAMIDOPROPYL DIMETHYLAMINE	356
05C - Hair Straighteners	STEARAMIDOPROPYL DIMETHYLAMINE	2
05E - Rinses (non-coloring)	STEARAMIDOPROPYL DIMETHYLAMINE	1
05F - Shampoos (non-coloring)	STEARAMIDOPROPYL DIMETHYLAMINE	10
05G - Tonics, Dressings, and Other Hair Grooming Aids	STEARAMIDOPROPYL DIMETHYLAMINE	44
05I - Other Hair Preparations	STEARAMIDOPROPYL DIMETHYLAMINE	18
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	STEARAMIDOPROPYL DIMETHYLAMINE	73
06B - Hair Tints	STEARAMIDOPROPYL DIMETHYLAMINE	1
06C - Hair Rinses (coloring)	STEARAMIDOPROPYL DIMETHYLAMINE	5
06H - Other Hair Coloring Preparation	STEARAMIDOPROPYL DIMETHYLAMINE	15
11E - Shaving Cream	STEARAMIDOPROPYL DIMETHYLAMINE	3
12A - Cleansing	STEARAMIDOPROPYL DIMETHYLAMINE	1
12D - Body and Hand (exc shave)	STEARAMIDOPROPYL DIMETHYLAMINE	2
12F - Moisturizing	STEARAMIDOPROPYL DIMETHYLAMINE	17
12G - Night	STEARAMIDOPROPYL DIMETHYLAMINE	1
12J - Other Skin Care Preps	STEARAMIDOPROPYL DIMETHYLAMINE	1

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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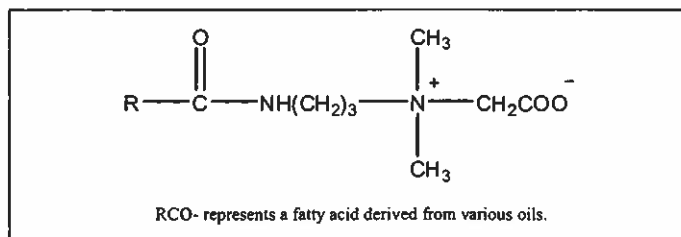


Figure 1. Amidopropyl betaine.

- 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 Ingredients²

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 <i>Prunus armeniaca</i> (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 <i>Persea gratissima</i> (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 <i>Orbignya oleifera</i> (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	None
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	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
		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. 657350 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 (<i>Theobroma grandiflorum</i>).	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
Meadowfoamidopropyl betaine (CAS 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 review with the myr- istates 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 <i>Avena sativa</i> (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 I. (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 butteramidopropyl betaine (CAS no. not found)	The zwitterion that conforms generally to the structure in Figure 1, where RCO- represents the fatty acids derived from <i>Butyrospermum parkii</i> (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
Undecylenamidopropyl 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 Betaines²

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-dimethyl-3-[(1-oxococonut)amino]-, hydroxide, inner salt
Almondamidopropyl betaine	Quaternary ammonium compounds (carboxymethyl)(3-cocoamidopropyl)dimethyl, hydroxides, inner salts
	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
Apricotamidopropyl betaine	Quaternary ammonium compounds (carboxymethyl)(3 almondamidopropyl) dimethyl, hydroxide, inner salt
	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
Avocadamidopropyl betaine	1 propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxoapricot)amino], hydroxide, inner salt
	Quaternary ammonium compounds (carboxymethyl)(3 apricotamidopropyl) dimethyl, hydroxide, inner salt
	Avocado amide propylbetaine
	Avocadoamidopropyl dimethyl glycine
	N(carboxymethyl) N,N dimethyl 3 [(1 oxoavocado)amino] 1 propanaminium hydroxide, inner salt
Babassuamidopropyl betaine	1 propanaminium, N(carboxymethyl) N,N dimethyl 3 [(1 oxoavocado)amino], hydroxide, inner salt
	Quaternary ammonium compounds (carboxymethyl)(3 avocadoamidopropyl) dimethyl, hydroxide, inner salt
	Babassu amide propylbetaine
	Babassuamidopropyl dimethyl glycine
	N (carboxymethyl) N,N dimethyl 3 [(1 oxobabassu)amino] 1 propanaminium hydroxide, inner salt
Behenamidopropyl betaine	1 propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxobabassu)amino], hydroxide, inner salt
	Quaternary ammonium compounds (carboxymethyl)(3 babassuamidopropyl) dimethyl, hydroxide, inner salt
	Behenamide propylbetaine
	Behenamidopropyl dimethyl glycine
	1 propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxobehenyl)amino], hydroxide, inner salt
Canolamidopropyl betaine	1 propanaminium, N(carboxymethyl) N,N dimethyl 3 [(1 oxodocosanyl)amino], hydroxide, inner salt
	Quaternary ammonium compounds (carboxymethyl)(3 behenamidopropyl) dimethyl, hydroxide, inner salt
	None found.
	Capryl/Capramidopropyl betaine
	None found.
Cupuassuamidopropyl betaine	Coco/oleamidopropyl betaine
	None found.
	Coco/sunfloweramidopropyl betaine
	1 Propanaminium, 3 amino N(carboxymethyl) N,N dimethyl, N (C8 18 and C18 Unsats. Acyl) derivs, hydroxides, inner salts
	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
	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
Lauramidopropyl betaine	Glycine, (3 lauramidopropyl)diemthylbetaine
	Lauroyl amide propyldimethyl glycine solution 1 propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxododecyl)Amino], hydroxide, inner salt
	None found.
	Meadowfoamidopropyl 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 N (carboxymethyl) N,N dimethyl 3 [(1 oxoolive)amino] 1 propanaminium hydroxide, inner salt
Olivamidopropyl betaine	Olivamidopropyl dimethyl glycine Olive amide propylbetaine 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxoolive)amino], hydroxide, inner salt Quaternary ammonium compounds (carboxymethyl)(3 oliveamidopropyl) dimethyl, hydroxide, inner salt
Palmamidopropyl betaine	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 Pentecamine (INN) 1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxohexadecyl)amino], hydroxide, inner salt N (carboxymethyl) N,N dimethyl 3 [(1 oxopalm kernel)amino] 1 propanaminium hydroxide, inner salt
Palm Kernelamidopropyl betaine	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 N (carboxymethyl) N,N dimethyl 3 [(1 oxoricinoleyl)amino] 1 propanaminium hydroxide, inner salt
Ricinoleamidopropyl betaine	1 Propanaminium, N (carboxymethyl) N,N dimethyl 3 [(1 oxoricinoleyl)amino], hydroxide, inner salt Propyl betaine ricinoleate amide solution Ricinoleamidopropyl dimethyl glycine 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
Sesamidopropyl betaine	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 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
Undecylenamidopropyl betaine	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 CAPB⁵

Color	Clear pale yellow liquid
Odor	Faint
pH	4.6-5.6
Water content	62%-66%
NaCl	4.6%-5.6%
Active materials (100 - H ₂ O - 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 undecylenamidopropyl 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, avocamidopropyl betaine, behenamidopropyl betaine, canolamidopropyl betaine, coco/sunfloweramidopropyl betaine, cupuasamidopropyl betaine, isostearamidopropyl betaine, MF betaine, milkamidopropyl betaine, minkamidopropyl betaine, oleamidopropyl 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

^aNatural 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									
Heptadecanoic (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)										
Eicosenoic (C20:1)	0.6									
Other							12-13.5 (unknown saturated acids)			0-1.2 (C20-C22 saturated acids)
Cholesterol, arachidonic acid, elaidic acid, and vaccenic acid									Small quantities	

the aerodynamic diameter, d_a , defined as the diameter of a sphere of unit density possessing the same terminal settling velocity as the particle in question. These authors reported a mean aerodynamic diameter of $4.25 \pm 1.5 \mu\text{m}$ 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

$\geq 80 \mu\text{m}$.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

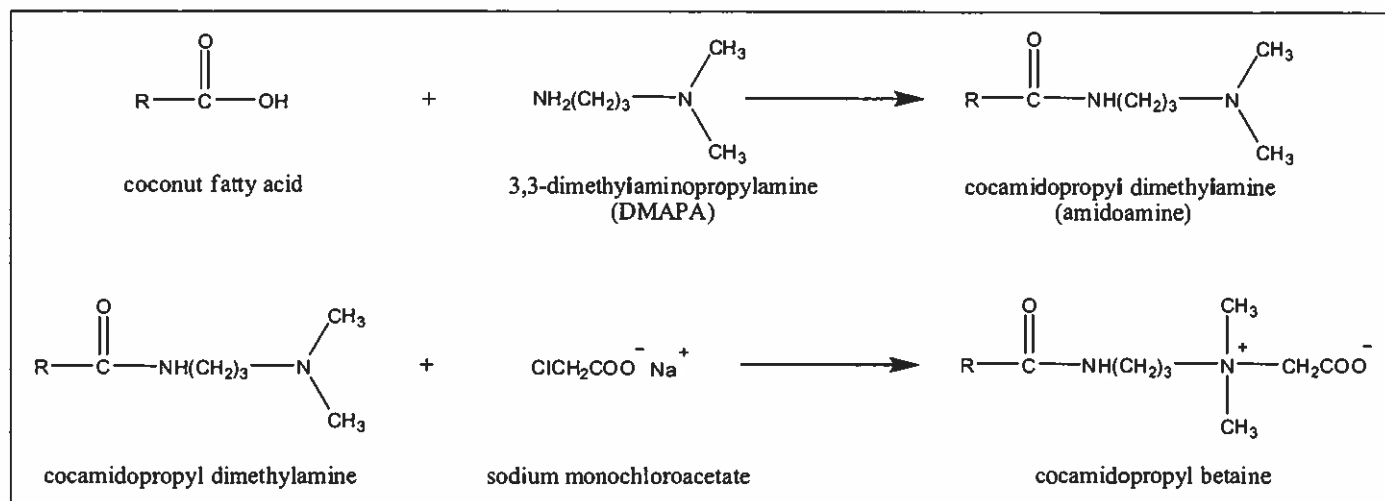


Figure 2. Reaction process of cocamidopropyl betaine (R represents the coconut fatty acid chain that varies between C-8 and C-18).

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 LD₅₀ 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 LD₅₀ 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 LD₅₀ 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 LD₅₀ 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/Capramidopropyl Betaine		Coco/Oleamidopropyl Betaine		Laureamidopropyl 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	NR	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}

	Oatamidopropyl 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 (%)	No. of Uses 2010	Conc. of Use 2010 (%)	No. of Uses 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	NR	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 LD₅₀ 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 LD₅₀ 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 LD₅₀ 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 ± 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 EC₃ 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 × 10³ µg/cm²]. 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 aqueous sol. of CAPB	93	Open application HRIPT	No sensitization	53
0.3% active CAPB in formulation	100	HRIPT	No sensitization	54
1.5% active aqueous 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 = $7.7 \times 10^2 \mu\text{g}/\text{cm}^2$].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 = $2.5 \times 10^2 \mu\text{g}/\text{cm}^2$ 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 = $5.8 \times 10^1 \mu\text{g}/\text{cm}^2$ at 1.5%, $1.2 \times 10^2 \mu\text{g}/\text{cm}^2$ 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 = $5.1 \mu\text{g}/\text{cm}^2$]. 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 = $2.5 \mu\text{g}/\text{cm}^2$]. After the induction phase ($3 \times$ 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 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 = $4.9 \times 10^2 \mu\text{g}/\text{cm}^2$]. 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 = $2.3 \times 10^1 \mu\text{g}/\text{cm}^2$]. 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/capramidopropyl 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 = $2.8 \times 10^2 \mu\text{g}/\text{cm}^2$]. 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 = $7.6 \times 10^{-1} \mu\text{g}/\text{cm}^2$].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 $\mu\text{L}/\text{plate}$. The CAPB is toxic above 0.3 $\mu\text{L}/\text{plate}$. 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 $\mu\text{L}/\text{plate}$ 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 $\mu\text{g}/\text{plate}$.³⁵ Positive controls were *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine (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 $\mu\text{L}/\text{plate}$ 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 $\mu\text{g}/\text{plate}$ without S-9 activation and at 4, 16, 64, 256, and 1024 $\mu\text{g}/\text{plate}$ 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 \pm 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 $\mu\text{L}/\text{mL}$. 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 Epplery 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 = $6.1 \times 10^2 \mu\text{g}/\text{cm}^2$]. 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 = $1.5 \times 10^2 \mu\text{g}/\text{cm}^2$]. 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 cm² patch on the clipped skin of the left shoulder for a period of 6 hours. [Estimated dose/unit area = $2.5 \times 10^4 \mu\text{g}/\text{cm}^2$]. 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 ≥ 0.5 at 24 hours after the removal of the patch. After 48 hours, 6 animals had a reaction ≥ 0.5 . Three out of 10 animals had a reaction score of 2. At the second challenge, 7 guinea pigs had a score of ≥ 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 ≥ 1 at 24 hours after patch removal. These scores 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 ≥ 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 ≥ 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 [³H] 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 (EC₃) 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 ≤ 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 [³H] 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 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 EC₃ was calculated at 1.4%. The positive control group had expected results and validated the study. The study concluded that stearamidopropyl 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 ³H-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 EC₃ 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/cm²]. 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 surfactants) 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 $\mu\text{g}/\text{cm}^2$ and 180 $\mu\text{g}/\text{cm}^2$, 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 ($\text{AELs} = \text{WoE NESIL} \times \text{SAF}^{-1}$), and consumer exposure level (CEL) that are appropriate for each product category. According to the QRA method, the ratio of $\text{AEL} \times \text{CEL}^{-1}$ 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 ($\text{AEL} \times \text{CEL}^{-1} = 0.15$). 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 of Raw Material	Product Exposure ^c (μg/cm ²)	CAPB Exposure (μg/cm ²)	AA CEL (μg/cm ²)	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 LD₅₀ to be 8.55 g/kg. The oral LD₅₀ of 30% active CAPB in albino rats of an unspecified strain was 4.9 g/kg. The acute oral LD₅₀ 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 LD₅₀ 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 ($\mu\text{g}/\text{cm}^2$)	CAPB Exposure ($\mu\text{g}/\text{cm}^2$)	DMAPA CEL ($\mu\text{g}/\text{cm}^2$)	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 $\mu\text{g}/\text{cm}^2$.

^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 PIs 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 than 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,
- 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 kemelamidopropyl 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 ($\sim 38 \mu\text{m}$) and pump hair sprays ($>80 \mu\text{m}$) was large compared to respirable particulate sizes ($\leq 10 \mu\text{m}$).

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,
- meadowfoamidopropyl 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: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: April 24, 2014

SUBJECT: Skin Sensitization Quantitative Risk Assessment on Stearamidopropyl Dimethylamine

Stearamidopropyl Dimethylamine Skin Sensitization Quantitative Risk Assessment

Representing Views of the CIR Science and Support Committee
23 April 2014

Conclusions: The Cosmetic Ingredient Review (CIR) Science and Support Committee, at the request of the CIR staff have drafted a quantitative risk assessment (QRA) for skin sensitization of stearamidopropyl dimethylamine (SAPDMA) to support the CIR Expert Panel review of Fatty Acid Amidopropyl Dimethylamines. The CIR Science and Support Committee agree with the Tentative Report that concludes a Weight of the Evidence No Expected Sensitization Induction Level (WoE NESIL) for SAPDMA of 1,000 $\mu\text{g}/\text{cm}^2$. The safety data for skin sensitization in the Tentative Report is summarized here and a QRA for skin sensitization is provided in support of some, but not all current use levels of stearamidopropyl dimethylamine in cosmetic products.

The testing data are summarized in this document and priority has been given to the human skin sensitization test data for assigning the WoE NESIL, as is customary (ECETOC Monograph No. 32, Use of Human Data in Hazard Classification for Irritation and Sensitization, 2002 and summarized in Kimber et al., 2001).

The CIR Science and Support Committee greatly appreciate the opportunity to provide input for the present evaluation and welcome the opportunity to provide further input if requested.

Background: Stearamidopropyl dimethylamine (SAPDMA) is the amidoamine that conforms generally to the structure shown in Figure 1. This amidoamine results from the reaction of DMAPA and stearic acid (CIR Safety Assessment of Fatty Acid Amidopropyl Dimethylamines as Used in Cosmetics, Tentative Report for Public Comment, March 31, 2014). Based on the Tentative Report for Fatty Acid Amidopropyl Dimethylamines, SAPDMA has the highest number of cosmetic uses for this class of compounds and is used in non-coloring hair conditioners up to 5%.

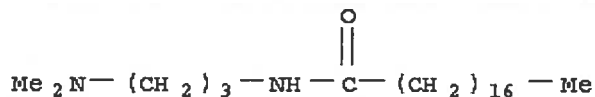


Figure 1. Stearamidopropyl dimethylamine (CAS no. 7651-02-7)

Human sensitization data on SAPDMA: Table 6 of the Tentative Report lists 11 human repeat insult patch test (HRIPT) dermal sensitization studies for SAPDMA. All studies concluded that at the concentrations tested, SAPDMA did not induce sensitization, but in some cases produced skin irritation. For example, one HRIPT with 0.75% SAPDMA in a rinse-off hair conditioner, 2% dilution in deionized water produced erythema (++) and edema on the 6th induction patch, which was determined to be possible contact dermatitis. The dose of SAPDMA per unit area of this skin in this study was 15 $\mu\text{g}/\text{cm}^2$. Overall, the study concluded no sensitization. From the data provided in all 11 HRIPTs, the dose of SAPDMA per unit area of the skin tested ranged from 0.45 to 1,000 $\mu\text{g}/\text{cm}^2$. The highest dose tested (1,000 $\mu\text{g}/\text{cm}^2$) was with 2% SAPDMA in a hair conditioner with 0.2 g samples applied to 4 cm^2 semi-occlusive patches with 104 subjects completing and none demonstrating sensitization responses. This study was chosen for the WoE NESIL for QRA purposes. In addition, Table 7 of the Tentative Report describes a human HRIPT previously reported to the CIR Expert Panel. In brief, a dose of 187 $\mu\text{g}/\text{cm}^2$ applied

under Webril patches in 112 subjects did not result in skin sensitization, which is consistent with the data in Table 6.

Rodent sensitization data on SAPDMA: Table 6 of the Tentative Report lists a guinea pig maximization test with SAPDMA conducted in 10 guinea pigs. A concentration of 2.5% was used for intradermal induction, 1% for dermal induction, and 2% as a challenge concentration in paraffin oil. No sensitization occurred in the study. Table 7 lists 2 additional rodent studies that were previously submitted to the CIR Expert Panel. One Buehler guinea pig test was conducted with 1% SAPDMA in 80% ethanol 20% water applied for induction under occluded Hill Top chambers on 20 guinea pigs. While the results would have been considered negative (i.e., < 15% positive responses observed in test animals), the re-challenge results indicate a weak skin sensitization potency classification for SAPDMA. Table 7 also reported a mouse local lymph node assay (LLNA) for SAPDMA (TEGO AMID S 18 containing ≤ 20 ppm DMAPA). The stimulation index (SI) for 0.1, 0.5, 1, 2.5, and 5% concentrations of SAPDMA were 1.4, 2.1, 2.1, 5.8, and 3.9, respectively. The EC3 value was calculated as 1.4%, which translates to a threshold of $350 \mu\text{g}/\text{cm}^2$.

Summary of sensitization data and determination of WoE NESIL for SAPDMA: The data that are used to determine the sensitization potential of a material may be of variable quality and robustness. Therefore, it is recommended to use a weight of evidence approach considering all available data for the identification of a NESIL that can be used in the exposure based QRA process. The NESIL may be derived from human and animal data and is expressed as a dose per unit area (e.g., $\mu\text{g}/\text{cm}^2$) value.

For the determination of a WoE NESIL for SAPDMA, data from eleven Human Repeat Insult Patch Tests (HRIPT), one LLNA, one Buehler Guinea Pig test and one Guinea Pig Maximization Test were evaluated.

No skin responses indicative of skin sensitization were observed in any of the eleven HRIPTs. One of the HRIPTs was conducted with SAPDMA in a simple vehicle. In that study testing was conducted under occlusive conditions. Slight to moderate transient responses were observed during induction and five subjects had mild responses at the 24 hour challenge grading. The observed responses were considered to be indicative of skin irritation so SAPDMA was considered to be non-sensitizing under the conditions of the study. The remaining ten HRIPTs were conducted with SAPDMA as an ingredient in a product matrix (rinse-off and leave-in hair conditioners, pre-shave scrub, and a face and neck product) with some irritation responses and no skin sensitization reactions observed.

The LLNA for SAPDMA was positive with an EC3 value of 1.4% ($350 \mu\text{g}/\text{cm}^2$). However, 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 which persisted for 2 days in the 1% dose group and until treatment end in the 2.5% and 5% dose groups. The dose response curve was slightly irregular with the SI of the 5% dose group being lower than the SI of the 2.5% group. The poor dose response coupled with the observed irritation could have impacted the outcome of this study.

The results of the primary challenge in the SAPDMA Buehler test would have been considered negative but the re-challenge results indicate a weak skin sensitization potency classification for SAPDMA.

The results of the Guinea Pig Maximization test with 2.5% SAPDMA for intradermal induction and 1% for dermal induction indicate a no sensitization in the 10 guinea pigs tested.

In deriving a WoE NESIL, when there is a significant discrepancy between a HRIPT NOEL and a LLNA EC3 value (e.g., around an order of magnitude or more), further consideration in setting the NESIL is required. In the case of SAPDMA, skin irritation may have been a confounding

factor in the LLNA. Since the dose levels use for induction and challenge in the Buehler test are derived on the basis of a pre-screen for irritation, the results observed in that test may be more reflective of the sensitizing potency of SAPDMA. The results from testing in several HRIPTs produced no contact allergic responses, although skin irritation was observed when testing was conducted under occlusive conditions. Taking these data into consideration, a WoE NESIL of 1,000 $\mu\text{g}/\text{cm}^2$ for SAPDMA would be appropriate for use in a QRA for skin sensitization. Since no sensitization was observed in the HRIPTs, the dose reported as the WoE NESIL reflects the highest concentration tested, not necessarily the highest achievable NOEL.

Example of how the WoE NESIL for SAPDMA is used in a QRA for Skin Sensitization :

Use of sensitization data in QRA for skin sensitization has been described earlier (Api et al., 2008). Using this approach, a QRA for SAPDMA present as a constituent at 5% in a hair conditioner product is provided in the table below. Although SAPDMA can be found in a range of product types, the QRA presented has been conducted on a hair conditioner as this product represents the highest concentration of use reported. The QRA for 5% SAPDMA in a hair conditioner demonstrates an adequate margin of safety and is supportive of continued use at this level in this product type.

WoE NESIL = Weight of Evidence No Expected Sensitization Induction Level for SAPDMA	1,000 $\mu\text{g}/\text{cm}^2$ (based on HRIPT data and supported by rodent data)
SAF = Sensitization Assessment Factor	30 (10X inter-individual, 1X matrix, 3X use conditions). The default matrix SAF of 3X is reduced in this case to 1X since the HRIPT was done in a hair conditioner matrix. The default 3X use condition SAF is because the area is the head which is highly follicular and the scalp which is more permeable.
AEL = Acceptable Exposure Level = (WoE NESIL/SAF)	33 $\mu\text{g}/\text{cm}^2$
Product Exposure	0.20 $\text{mg}/\text{cm}^2/\text{day}$ of conditioner (CTFA 90 th percentile data as noted for rinse-off conditioners as reported in Api et al., 2008).
Concentration of SAPDMA in the product	SAPDMA is present in the conditioner at 5%, which is the maximum level listed in the 2014 Tentative CIR for Fatty Acid Amidopropyl Dimethylamines.
CEL = Consumer Exposure Level	10 $\mu\text{g}/\text{cm}^2$ [based on 5% of 0.20 mg/cm^2]
Risk Assessment	Acceptable risk because AEL > CEL; MOS = Margin of Safety for sensitization = AEL/CEL = 3.

QRA calculations for all product categories based on the Council concentration of use survey are in the attached spreadsheet.

Recommendation to CIR Expert Panel on SAPDMA with respect to skin sensitization potential : The CIR Science and Support Committee has provided a QRA for skin sensitization potential of SAPDMA as currently used in cosmetic products. The QRA demonstrates a favorable margin of safety for continued safe use of SAPDMA at present levels in hair conditioners. Based on the most current VCRP product use and concentration data some product categories are supported by the QRA and some are not:

Product categories supported with current use levels:

- Hair conditioners
- Rinses (non-coloring)
- Shampoos (non-coloring)
- Other hair preparations (non-coloring) rinse-off
- Foundations
- Bath soaps and detergents
- Preshave lotions (all types)
- Skin cleansing (cold creams, cleansing lotions, liquids and pads)
- Other skin care products

Product categories NOT supported with current use levels (i.e., inadequate margin of safety) :

- Eye lotion
- Eye make-up remover
- Cologne and toilet waters
- Tonics, dressings and other hair grooming aids
- Hair dyes and colors
- Face powders
- Lipsticks
- Makeup bases
- Aftershave lotions
- Face and neck creams, lotions, powders
- Body and hand cream lotions and powders
- Moisturizers
- Indoor tanning products

Note that the NESIL is based on the highest dose per unit area in the HRIPTs that did not induce a sensitization response (i.e., a free-standing NOEL). The true threshold for induction of sensitization may or may not be higher than the NESIL chosen. Regardless, further justification is needed for the current use levels of SAPDMA in the product categories not supported by the QRA.

References :

CIR Safety Assessment of Fatty Acid Amidopropyl Dimethylamines as Used in Cosmetics, Tentative Report for Public Comment, March 31, 2014

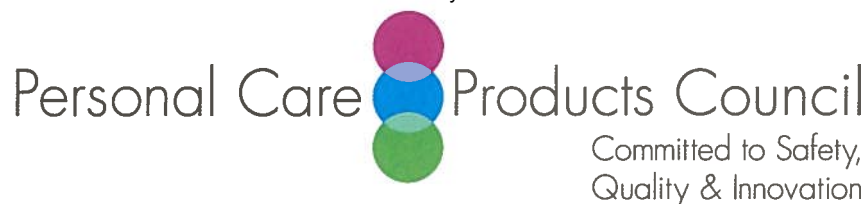
Api, AM, Basketter, DA, Cadby, PA, Cano, M-F, Ellis, G, Gerberick, GF, Griem, P, McNamee, PM, Ryan, CA, and Safford, R (2008). Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regulatory Toxicology and Pharmacology* 52:3-23.

ECETOC Monograph No. 32, Use of Human Data in Hazard Classification for Irritation and Sensitization, ISSN-0773-6347-32, Brussels, July 2002

Kimber, I, Basketter, DA, Butler, M, Gamer, A, Garrigue, JL, Ilea, L, Newsome, C, Roggeband, R, Steiling, W, Stropp, G, Waterman, S, and Wienmann, C (2001). Skin sensitization testing in potency and risk assessment. *Toxicological Science* 59:198-208.

Product Category	Max Use (%)	Product Exposure (µg/cm ²)	SAPDMA CEL (µg/cm ²)	SAPDMA AEL	SAF	NESIL (µg/cm ²)	AEL/CEL	Reference for Exposure
Eye lotion	1.8	2170	39.06	3.33	300.00	1000.00	0.09	Api et al., 2008 Eye products.
Eye makeup remover	1.5	900	13.50	10.00	100.00	1000.00	0.74	Api et al., 2008 Make-up remover.
Cologne and toilet waters	1.8	17700	318.60	10.00	100.00	1000.00	0.03	Api et al., 2008 Hydroalcohols for unshaved skin
Hair conditioners	5	200	10.00	10.00	100.00	1000.00	1.00	Api et al., 2008 Hair conditioners.
Rinses (noncoloring)	1	170	1.70	10.00	100.00	1000.00	5.88	Api et al., 2008 Shampoos.
Shampoos (noncoloring)	2	170	3.40	33.33	30.00	1000.00	9.80	Api et al., 2008 Shampoos.
Tonics, dressings and other hair products	3	990	29.70	10.00	100.00	1000.00	0.34	Api et al., 2008 Hair styling aids
Other hair preparations (non-coloring)	0.5	200	1.00	10	100	1000.00	10.00	IFRA RIFM QRA Information Booklet version 6.0 July 2011 (C)
Hair dyes and colors	2	1000	20.00	10.00	100.00	1000.00	0.50	IFRA RIFM QRA Information Booklet version 6.0 July 2011 (C)
Face powders	1.7	1000	17.00	10.00	100.00	1000.00	0.59	IFRA RIFM QRA Information Booklet version 6.0 July 2011 (C)
Foundations	0.25	3170	7.93	10.00	100.00	1000.00	1.26	Api et al., 2008 Women's facial liquid makeup.
Lipsticks	1.7	11460	194.82	3.33	300.00	1000.00	0.02	Api et al., 2008 Lip products
Makeup bases	1.6	4200	67.20	10.00	100.00	1000.00	0.15	IFRA RIFM QRA Information Booklet version 6.0 July 2011 (C)
Bath soaps and detergents	1.8	10	0.18	10.00	100.00	1000.00	55.56	Api et al., 2008 Bath foams, gels, mousses.
Aftershave lotions	2	2210	44.20	10.00	100.00	1000.00	0.23	Api et al., 2008 Hydroalcoholic products for shaved skin
Pre shave lotions (all types)	0.05	2200	1.10	10.00	100.00	1000.00	9.09	IFRA RIFM QRA Information Booklet version 6.0 July 2011 (C)
Skin cleansing (cold creams, cleansers)	0.07	900	0.63	10.00	100.00	1000.00	15.87	Api et al., 2008 Make-up remover.
Face and neck creams, lotions, powders	1.2	2700	32.40	10.00	100.00	1000.00	0.31	Api et al., 2008 Women's facial cream
Body and hand creams, lotions and perfumes	1.5	1120	16.80	3.33	300.00	1000.00	0.20	Api et al., 2008 Body creams and lotions
Moisturizers	1	2700	27.00	10.00	100.00	1000.00	0.37	Api et al., 2008 Women's facial cream
Other skin care products	0.1	2200	2.20	10.00	100.00	1000.00	4.55	IFRA RIFM QRA Information Booklet version 6.0 July 2011 (C)
Indoor tanning preparations	2	2200	44.00	10.00	100.00	1000.00	0.23	IFRA RIFM QRA Information Booklet version 6.0 July 2011 (C)

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: March 10, 2014

SUBJECT: Comments on the Draft Report Prepared for the March 17-18, 2014 Meeting:
Safety Assessment of Fatty Acid Amidopropyl Dimethylamines as Used in
Cosmetics

Key Issue

Draft Conclusion - As there appears to be sufficient data to support the safety of Stearamidopropyl Dimethylamine (the ingredient with the most use), the draft conclusion of insufficient data for all the ingredients in this report is not appropriate.

Additional Comments

- p.1 - Please delete the word "private" when describing the companies submitting information to the European Chemicals Agency. By describing a company as "private", a reader may interpret this to mean that companies that are publically held are not included. For the purposes of information submission to the European Chemicals Agency, a distinction between private and publically held companies is not necessary.
- p.3 - In the Cosmetic Use section, it should be made clear that it is not known whether or not the cologne and indoor tanning products are sprays. The 2% use concentration was reported in an indoor tanning preparation, the form was not stated.
- p.4 - In the description of the 14-day oral study, please state the organs that were examined microscopically. It is especially helpful to list which reproductive organs were examined.
- p.4 - In the description of the dermal 90-day study, please correct "distilled, 30%/70% ethanol/water" as distilled probably only refers to the water not the mixture. The description of the methods of this study should indicate that collars were used to prevent oral exposure.
- p.5 - In the Reproductive and Developmental Toxicity study, please list the reproductive organs that were examined in the 90-day dermal study in rabbits.
- p.5 - Were the rabbits collared in the dermal developmental toxicity study?

- p.7 - Did reference 32 provide any information about the identity of the “amidoamine” used for testing?
- p.7 - Please provide references in the paragraph describing the dermal irritation and sensitization studies. The concentrations tested are not clear. It would be clearer to state that a hair conditioner containing 2% Stearamidopropyl Dimethylamine was tested neat (or undiluted), as “at 2% neat” does not make sense.
- p.7 - Please revise the following: “Reactions were especially prevalent when applied...” - what was applied? Based on the current sentence structure, “reactions” were applied.
- p.20, Table 3a - The meaning of the numbers in parentheses is not clear.



Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: April 24, 2014

SUBJECT: Comments on the Tentative Report: Safety Assessment of Fatty Acid
Amidopropyl Dimethylamines as Used in Cosmetics

Key Issue

In addition to the quantitative risk assessment (QRA) on the sensitization potential of Stearamidopropyl Dimethylamine that was recently provided by the CIR SSC, the QRAs on amidoamine (Cocamidopropyl Dimethylamine) and DMAPA provided for the CAPB CIR report should also be summarized in this report. Presentation of the NESILs from all three QRAs (1000 $\mu\text{g}/\text{cm}^2$ Stearamidopropyl Dimethylamine; 425 $\mu\text{g}/\text{cm}^2$ amidoamine; 180 $\mu\text{g}/\text{cm}^2$ DMAPA) is especially important. The Discussion of the CIR report should also include a more robust presentation of how these NESIL values should be used to determine safe levels of these ingredients in specific product categories. The NESIL on Stearamidopropyl Dimethylamine should only be applied to compounds in which the fatty acid group is C18 or larger, while the NESIL for amidoamine should be applied to the smaller compounds. The Discussion should also make it clear that the DMAPA content of the ingredient must also be considered when determining the sensitization potential of these ingredients, and must be quite low to be below the NESIL of 180 $\mu\text{g}/\text{cm}^2$.

Additional Comments

- p.9 - In the Discussion, please include the highest use concentration of CAPB and the product category for which 0.01% DMAPA was found to be an acceptable level according to the QRA.
- p.11-12, Table 3a - The process for preparing the cosmetic use tables should be more transparent. The methodology indicating which FDA product categories are mapped to which CIR product categories should be available on CIR's website.

If a footnote does not apply to all of the information in a row, it should not be associated with the row heading. For example, footnote 6: Not specified whether a powder or a spray, so the information is captured for both categories of incidental inhalation. This is not true as the 1% concentration of Behenamidopropyl Dimethylamine associated with hair grooming aids is not also presented as a possible powder product.

When none of the ingredients have reported uses in deodorant products, why is it necessary to have three rows devoted to deodorant products all with NR in each column? The last row of the deodorant category - Reported as Not Spray has the footnote 3, Use in a spray product has been reported in response to a survey conducted by the Council. This does not make sense.

The Council survey reported use of 1% Oleamidopropyl Dimethylamine in a face and neck product (skin care product), but the leave-on category only indicates concentrations of 0.0015-0.13%.

The Council's survey reported use of Stearamidopropyl Dimethylamine in the face powder makeup category. Why is this product in the row titled Incidental Inhalation-Powder? (which has the footnote: It is possible these products may be powders, but it is not specified whether the reported uses are powders)? This is a powder product.