Safety Assessment of Alkonium Clays as Used in Cosmetics

Status:	Revised Tentative Report for Panel Review
Release Date:	March 7, 2016
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The 2016 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, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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Cosmetic Ingredient Review

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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: March 7, 2016

Subject: Safety Assessment of Alkonium Clays As Used In Cosmetics

Attached is the revised draft final report of Alkonium Clays as used in cosmetics. [*alkcly032016Rep*] At the December, 2015 meeting, the Panel issued a tentative report with a revised conclusion of safe when formulated to be non-irritating. This conclusion reflects a change from the previously issued insufficient data conclusion because of new data that were received and reviewed.

No new data have been submitted since the December 2015 Panel meeting. Council comments were addressed. [*alkcly032016PCPC*]

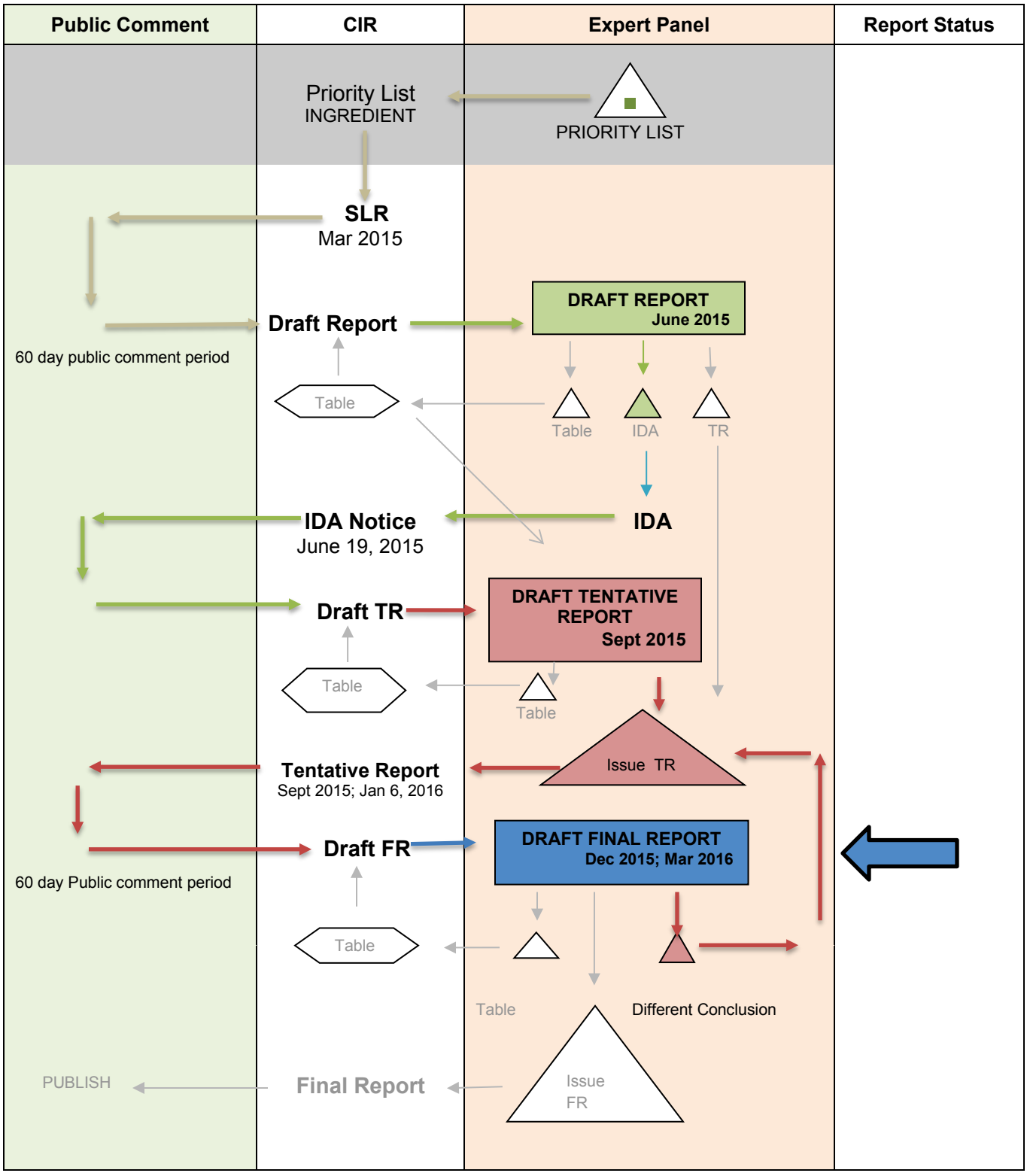
2016 VCRP data have been incorporated into the report. The number of uses of Stearalkonium Bentonite has decreased by 35, mostly in nail products. Quaternium-90 Bentonite increased by 1 use. There were still no reported uses in the VCRP for the rest of the ingredients in this report. [*alkcly032016FDA*]

The Panel should review the Discussion to make sure it adequately addresses their concerns, and be prepared to issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Alkonium Clays

MEETING Mar 2016



Report History – Alkonium Clays

June, 2014 – This group of ingredients was added to the priority list.

March, 2015 – SLR was posted on the CIR website with a request for more data.

- Chemical and physical properties;
- Impurities data;
- Toxicokinetic data, specifically dermal absorption of these ingredients; if these ingredients were to have appreciable dermal absorption or if toxicokinetic assays are not possible, oral toxicity data, including reproductive/developmental toxicity and carcinogenicity data, are needed, as are genotoxicity data; these data may not be crucial if these ingredients have no appreciable dermal penetration, however, if they were available, they would improve the resulting safety assessment;
- Oral, inhalation, and/or dermal toxicity data;
- Dermal, ocular, and/or other mucous membrane irritation and sensitization data; and
- Any other relevant safety information that may be available.

June, 2015 – The Panel issued an Insufficient Data Announcement.

- Particle size distributions relevant for assessing potential inhalation exposures
- Percent (by weight) alkonium cation in these ingredients and the percent (by weight) releasable/exchangeable in solution
- Inhalation data at concentration of use (2.2% in powders and 3.2% in sprays)
- Ocular irritation at concentration of use, if available

September, 2015 – The Panel issued a Tentative Report with an insufficient data conclusion. The data needs were:

- Particle size distributions relevant for assessing potential repeated inhalation exposures of powders
- Percent alkonium cation in these ingredients that are releasable/exchangeable in solution
- Repeated dose inhalation data at concentration of use (3.2%)
- Ocular irritation at concentration of use

December, 2015 – The Panel examined the additional data (dermal irritation and sensitization data on a mascara containing quaternium-90 bentonite; confirmation that a face product containing quaternium-90 bentonite at 0.88% is a lotion and is not a powder). The Panel changed the conclusion and issued a revised tentative report for public comment with the conclusion that these 8 alkonium clays are safe when formulated to be non-irritating.

March, 2016 – The Panel is to issue a Final Report.

Alkonium Clays Data Profile for ***March*, 2016**. Writer – Lill Becker																						
	ADME			Acute toxicity			Repeated dose toxicity			Irritation						Sensitization						
	Dermal Pen	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Animal	Ocular Human	Ocular In Vitro	Dermal Animal	Dermal Human	Dermal In Vitro	Animal	Human	In Vitro	Repro/Devel	Genotoxicity	Carcinogenicity	Phototoxicity
Benzalkonium montmorillonite																						
Benzalkonium sepiolite																						
Hydrogenated tallowalkonium bentonite																						
Quaternium-18/ benzalkonium bentonite																						
Quaternium-90 bentonite			X								X	X		X			X					
Quaternium-90 montmorillonite			X														X					
Quaternium-90 sepiolite			X														X					
Stearalkonium bentonite		est	X	X	X		X						X			X	X			X		
Read across																						
Benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay				X		X																
Quatemium-18 bentonite				X		X	X	X					X			X	X			X		
Stearalkonium hectorite								X														
Dihydrogenated tallow benzylmonium hectorite																			X			

Est=estimated

Search Strategy – Alkonium Clays

SciFinder – Substance search. 109 hits. None useful.

INCI names and CAS nos. 109 hits. Removed patents – 22 hits. None useful.

"Alkonium clays" – 2 hits. None useful.

"Bentonite toxicity" – 4 hits. 1 ordered

"Montmorillonite toxicity" – 282 hits. Removed patents – 206 hits. English – 176 hits. 16 ordered.

"Sepiolite toxicity" – 73 hits. Removed patents – 48 hits. English – 33 hits. Ordered 3.

HPVIS – INCI names and CAS nos. No hits.

Google - INCI names and CAS nos. A few MSDS sheets; NICNAS 2013 on Stearalkonium Bentonite.

Second Google search turned up 2 2015 NICNAS reports on:

- Benzalkonium Montmorillonite, Quaternium-90 Montmorillonite, and Hydrogenated Tallowalkonium Bentonite
- Benzalkonium Sepiolite and Quaternium-90 Sepiolite

ECHA – CAS Nos and INCI names. 1 hit. Searched downloaded database for montmorillonite (2 hits), sepiolite (no hits), and bentonite (1 hit). Only the montmorillonite was useful for read across. Most of the data had sparse details and not useful. Used what was relevant.

NTP – INCI names and CAS Nos. No hits.

Transcripts – Alkonium Clays
December, 2015

Dr. Marks' Team

DR. MARKS: …Next, alkonium clays. In September, the Panel issued a tentative report with an insufficient data conclusion. In Lillian's memo, she bullet points the data that were needed, particle size, percent alkonium cation, the inhalation data for repeat dose, ocular irritation, and confirmation that these ingredients are not used for powders.

We had a lot of these addressed both in Lillian's report and also in Wave 2. Ron, Tom? Now can we change the conclusion, safe when formulated to be non-irritating? Can we issue a revised tentative report with that conclusion? Tom and Ron? Were all the data needs addressed and can we move forward to that conclusion?

DR. SLAGA: (inaudible)

DR. SHANK: Correct.

DR. MARKS: No face powder, don't need inhalation, but the CIR SSC memo on page 38 addresses it and said powder shouldn't be an issue, if I interpreted that memo correctly. Is that right, Jay? You did calculations which suggested powder would be safe for inhalation.

DR. ANSELL: I'm not exactly sure where we want to discuss this, but the issue of powders and inhalation potential was raised several times through the meeting, including within the context of this report.

We did a literature search and came up with what we believed to be conservative quantifiable measurements of inhalation potential of powders in actual applications, and find that the exposure, we believe, would fall well below the threshold of toxicologic concern.

I know Ivan has reviewed the discussion and prepared his own cover memo. I don't know whether this is the right place or not.

DR. GILL: I had asked the Panel to discuss it during this ingredient.

DR. MARKS: It comes up here and then we have to address the memo, even though in this report it appears these aren't being used as powders. That was the thing you brought up, Tom. It's not directly relevant with this. My initial impression was should the boilerplate be changed.

DR. BOYER: The issue really became prominent at the last meeting during the discussion of the alkonium clays, during the discussion of this ingredient. The issues were, at least from my perspective, is the boilerplate sufficient, does it address the potential for inhalation exposure from a powder product sufficiently based on what we know about that kind of exposure.

Also, there was a question raised about the potential for particle overload through inhalation of respirable particles, tremendous concentrations. There are sections in our current boilerplate that address both of those. The question is are those sufficient or should we make some changes there.

I think that the exercise the SCC did showed very clearly that any inhalation through the use of a powder, even a talcum powder, which is very dry and is likely to release some, not insignificant but not respirable material. I think they showed very plainly the overall exposure would be very, very small.

DR. HILL: I know how I was thinking of this, and I will just preface it by saying my first take on this ingredient class was no problem, and I was going from the HRIPT data, but then Dan raised the issue can we exchange out any of these substances to any appreciable extent.

I think on the one hand, that exchange probably doesn't occur in any case. Dan was reasonably looking for indication of that. The data we got don't tell us that answer because the way the study was done is not informative.

The sensitization was the only concern here in terms of toxicological endpoints, in

breathing a powder, where a class of compounds is known to be sometimes sensitizing and could be released in a way that causes that sensitization to occur. That is what I thought brought this all on with this particular ingredient class. I may be mistaken.

DR. BOYER: No, I think the issues are intertwined. If in fact the exposure was particles and significant, then the question becomes even at very small exposure, very tiny exposure, is there going to be an issue with respect to the potential for irritation, potential for release of something coming from the ingredient that might cause some respiratory issues.

DR. HILL: Right. I wasn't worried about irritation, only sensitization. I don't think you can get the kind of exposures that would cause irritation from the kinds of powder. I think that write up is spot on in that regard. You sure are not going to get enough particles to have any overload effect.

DR. MARKS: I think the plan of the discussion is do we need to bring the boilerplate back out and look at it and incorporate somehow the CIR SSC memo, which tests to the safety of powders. I have a feeling it will be lost in the minutes of this report, and should be referenced directly to that boilerplate.

Tom, Ron Shank, what are your feelings about this? Ivan, what do you think? This is a little different than just the leading two ingredients from the boilerplate that aren't being used. This has more thought and depth to it, perhaps the boilerplate should it come up in a future meeting addressing specific powders, but what is your feeling?

DR. BOYER: I think the boilerplate as it is written now, it's the best we can do with the information that we have been able to gather. I think it is appropriate. I can't think of any revisions that would improve it.

DR. MARKS: Why did powders come up as a discussion, why couldn't they just plop the boilerplate in? Then we had this big issue about --

DR. BOYER: For example, the alkonium clays, it seems like there was a significant chance that you would get some substantial particles if you were using face powder, for instance. The potential for sensitization if in fact you get enough inhalation exposure to those particles.

DR. MARKS: Jay?

DR. ANSELL: I think it's because the inhalation boilerplate is focused on aerosol, the control of aerosol.

DR. MARKS: It doesn't address powders.

DR. ANSELL: No. The conclusion comes out where we would come out, but I think it's so focused on particle size and control, it would be worth taking a look at.

There is a substantial discussion but the powders are not totally -- address potential exposure in the document, but the boilerplate --

DR. HILL: That is two different things. The document versus what we put in the report.

DR. MARKS: Exactly. I'm just thinking of the future, five years from now, powder could come up as an issue, or two years from now. It's in the boilerplate. We have addressed it. We reference the CIR SSC memo. We feel safe. It shouldn't come up as an issue.

DR. BOYER: I think perhaps when we look at the boilerplate, we might want to remove the part that seems to focus on aerosols as opposed to inhalation exposure.

DR. MARKS: What is your sense? Did you revisit the boilerplate?

DR. SHANK: No. It's based on particle. Aerodynamic properties and particles. That is very specific.

DR. MARKS: How do we capture in the future the powders are safe?

DR. SHANK: Powders are particles.

DR. HILL: The Panel noted that 95 to 99 percent of particles would not be respirable but in fact if there are no particles in the range that would be respirable, when you give a powder, why do we even have to say that. It suggests there is a safety hazard that doesn't exist maybe.

DR. BOYER: What you are reading refers specifically to the sprays, spray products.

DR. HILL: Why is that language even in here if that's the case, because it is in here, in the discussion.

DR. BOYER: We have a lot of information, a lot more information about what comes out of a spray product in terms of particle sizes and so forth. When it comes to a powder product, we can say things like don't expect there to be a lot of particulate release to the air because they usually are combined with some oils and so forth, they're compacted, and so on.

We don't have any real specific experimental data that addresses that except what the SCC found, a couple of papers on talcum powder. If you use that as a very conservative example of the level of exposure that consumers might receive through the use of very loose powdered product, even then, the exposures would be very, very small, at least compared to occupational standards, they are miniscule.

We do have more to say about what comes out of a spray. We could beef up in terms of the framework, add some suggestive language that might be incorporated when in fact we know a substance, an ingredient, is used in a loose powder product, like a face powder or baby powder. That's doable.

DR. HILL: I just crossed up what I said because the one paragraph is dealing with a potential aerosol suntan product and others, there is no powder here now, right?

DR. MARKS: So, what was the discussion in the memo is irrelevant, if we put that in the discussion, it is irrelevant.

DR. BOYER: For this particular ingredient, it's not an issue any more.

DR. MARKS: We also lose this robust discussion that powders are safe. It will be in the minutes of the meeting, but it won't be --

MS. BECKER: I'll make sure to extract it and send to Ivan.

DR. MARKS: Okay. We will see in a couple of years when this comes up again. (Laughter) Ivan and Lillian, I'll let you figure out how to do it. You heard Tom Slaga and Ron Shank say they're happy with the boilerplate as is.

DR. BOYER: I think what we will probably do is craft a little paragraph, the same thing as the other suggested passages.

DR. MARKS: We will let you bring that back to the Panel in the future. Okay. Tomorrow I'm going to move that we issue a revised tentative report with a conclusion of safe, formulated to be non-irritating for these alkonium clay ingredients.

DR. HILL: Assuming because the other one was the one that raised certain issues that I didn't raise because I was basing my deliberations on the HRIPT background, one way you could look at what we have here is the body of data supports Quat-90 and Stearalkonium and nobody else, how do you respond to that. What I would say about the exchange study is any exchange of an absorbed ion is dependent on ionic strength, and they did the thing in water, so I would have felt at least a little more comfortable if they had done the study in something similar to the mucous membrane, sweat, tears, or something.

I guess there is some salt content but not like sweat, where we actually would see something physiologically relevant in terms of the exchange. Again, I highly doubt it and we never saw anything with HRIPT that suggests this is a problem, but if they were genuinely worried about it, then the data only support Quat-90 and Stearalkonium.

DR. MARKS: Actually, this conclusion is our previous --

DR. HILL: I know.

DR. MARKS: We will deal with that tomorrow.

DR. HILL: I'm just tossing that out there.

DR. MARKS: I hear you.

DR. HILL: I'm basing mine on the HRIPT background context. Different clay but not that different.

DR. MARKS: We will see if the Belsito team is reassured with the data we have received and can move on. Does that sound good, Ron?

DR. SHANK: Yes.

DR. MARKS: Okay. Next is polymerized tetramethylcyclotetrasiloxanes.

Dr. Belsito's Team

DR. BELSITO: …Alkonium clays. So it's 5 of 3? Is this where we're going to have the powder discussion as well, or when were we going to do powder? Now, with alkonium clays? So did you want to take a 5-minute (file 00:52:19) break, be back at 3? Is that fair, because this is going to be two discussions; the powder and --

DR. SNYDER: Clay discussions, abbreviated, right? Because it's a lotion, it's not a powder.

DR. BELSITO: I thought we got into the powder discussion with clays as well.

DR. SNYDER: But we got it's way [wave] two data that said that the updated data survey that the -- not a powder, but it's a lotion.

DR. BOYER: That is correct. It's no longer an issue that is relevant, really, to the alkonium clays but it is an issue that it came out of the discussion of the last meeting of this particular ingredient group.

DR. BELSITO: But it's going to be a discussion then in the siloxanes, no?

DR. BOYER: Well we can probably -- If we roll one up with the discussion of the alkonium clays, that'll work just fine.

DR. BELSITO: Okay, so we'll be doing alkonium clays in Paris. It's 2:54, can we be back no later than 3:05? Does that work for everyone? Okay.

(Recess)

DR. BELSITO: The alkonium clays -- so we issued a tentative report for public comment on eight of these clays, and we requested data on the percent alkonium kati releasable in formulation, clarification that the excess quaternary ammonium compound not excess amines are present manufacturing process, and confirmation that quaturnium-90 is not used in face powders.

We're concerned about the 18-bentonite in face powders because the data in the report suggested the particle size was respirable, and so since that time we've been told it's not in a powder. It's in a liquid makeup. We have not been given any data on whether it's an amine or not that's in the product, and then I didn't know whether the information that we got on the strength of binding was adequate for (inaudible).

DR. LIEBLER: Oh, it's fine. Yes, there's a nice submission in Wave 2 that I think was the right measurement done the right way and (inaudible).

DR. BELSITO: It was water shaken in a beaker. That was (inaudible).

DR. LIEBLER: No, that's exactly what I wanted to know. How conditions and the right kind of measurement made, and my concern is satisfied.

DR. BELSITO: Okay, so then the only concern that remains is about whether it's an amine and we have a concern about nitrosation. That was Ron Hill's concern last -- it says under method of manufacture -- the second paragraph about montmorillonite salts. It says to remove any excess amine if an excess has been used, and Ron was concerned that if it was an amine the potential formation of nitrosamines. Wasn't that a data request?

DR. EISENMANN: No, actually not a data request, but it's been added as a data request. It was something that was discussed, and I think you can handle it in the discussion. I mean that was --

DR. BELSITO: I thought Ron asked it as a data request at that last meeting.

DR. EISENMANN: But it didn't end up as a data request.

DR. BELSITO: Why not?

DR. EISENMANN: I don't know.

DR. GILL: We wanted a clarification of the excess quaternary ammonium compounds, not excess amine in our data (inaudible).

DR. BELSITO: No, it says -- I thought that we asked was not in excess amine. In other words Ron wasn't clear. He thought that it might be a mistake; that it was a quaternary amine and not an amine in itself.

DR. EISENMANN: It was a 1940 reference, so I mean the language -- it might just be a language issue (inaudible).

DR. BELSITO: That was just a few years ago. (Laughter) For some of us (inaudible).

DR. LIEBLER: Yeah, I think as I'm looking at the transcript of our full-panel meeting where Ron brought this up. So Ron say "I think when they say amine they're meaning quaternary ammonium compound but I'm not certain of that, and we didn't get any more data on that. I would like to have that clarified because if it is an amine there might be an excess amine there. We worry about with at least a nitro amine issue."

The thing is there's no reason for them to put an amine into this. They're making these things by adding quaternary ammonium compounds. I mean I think it's very reasonable inference that that's simply a careless use of the term amine as opposed to quaternary ammonium.

DR. BELSITO: But you don't want the data?

DR. BERGFELD: On your Wave 2 there was some declaration of what was in it? I see it under something called element (inaudible).

DR. BELSITO: Yes, but it was essentially -- it said the same thing. It's an amine.

DR. BERGFELD: It said quaternary.

DR. LIEBLER: See --

DR. BERGFELD: Quaternary.

DR. LIEBLER: It is -- well, actually technically it's an ammonium.

DR. BERGFELD: Quaternary ammonium chloride --

DR. LIEBLER: I can imagine it easily being carelessly described by somebody as an amine.

DR. SNYDER: I thought Wave 2 took care of it, but I mean I didn't necessarily endorse that. Ron mentioned that in passing at the end of the discussion when I think we already -- had we already voted? Nah, we were just about to vote. Oh, and yeah, because right after Ron said that I said it strikes me as probably just a little imprecise. In other words, using the term amine, and Ron says I think that's the case but I would like to know that for sure, and then Wilma says all right, we'll have -- we have a motion. It was removed. We have a new motion. We have a second, so that's where we went. We never really added it to our list of data needs. Like I said, I think it's unnecessary.

DR. BELSITO: But it doesn't matter. Wave 2 hasn't clarified that.

DR. SNYDER: No.

DR. BELSITO: So how do we handle it at this point?

DR. SNYDER: Wave 2 -- it was -- I don't know if it was ever included in an insufficient data announcement.

DR. BELSITO: It wasn't according to Carl. Right, so --

DR. SNYDER: I think it's a non-issue.

DR. LIEBLER: So we met all the data needs for insufficiency, right?

DR. BELSITO: Well, assuming that's a non-issue, but then do we have to bring that non-issue into the discussion and say if this non-issue is real then it shouldn't be used in products where an N-nitrosamines can be formed?

DR. EISENMANN: Why don't you just say don't prepare the ingredients with excess amine. You're just using the -- you're understanding is just that quaternary ammonium compounds are being used.

DR. BELSITO: But maybe they aren't.

DR. EISENMANN: Well --

DR. LIEBLER: Al l right, if you -- I mean I don't think there's a good reason to object. I don't think there's a good reason to suspect (inaudible).

DR. BELSITO: Dan's the one that wanted the molecular weight on the polymers.

DR. LIEBLER: Hey, I was right that time.

DR. BELSITO: You're always right.

DR. LIEBLER: No, ask Karen.

DR. BERGFELD: His wife. (Laughter)

DR. SNYDER: So, this is a final.

DR. BELSITO: Yes. No. We were insufficient before, so this is the tentative final.

DR. HELDRETH: Also note that the rest of that sentence says washing with water and alcohol to remove it -- I mean if you've got a primary -- secondary amine and alcohol and water, it's going to go. It's not going to sit there in a charged surface system, displace the quaternary salt, so even if they did have an amine around, that sentence talks about getting rid of it.

DR. SNYDER: I thought we got data on the free quaternary ammonium chloride released issue on Wave 2.

DR. BELSITO: Yes, but not on whether there was amine in the product. We didn't get that data.

DR. BERGFELD: Quaternary ammonium chloride.

DR. BELSITO: Here's the additional data we got on clay. We got updated concentration of use survey, and we got an assay measuring the amount of free quaternary ammonium chloride produced when alkonium clays with varying amounts of dimethyl dehydrogenated tallow are placed in water. That's it. So, we've got concentration of use. We've got the question Dan asked about how stable the ammonium compounds were within this clay stuff.

DR. SNYDER: So, we misstated our data needs, so we wanted the clarification that the excess quaternary ammonium is not excess --

DR. BELSITO: Well, that's what -- my understanding was that that's what Ron asked for and it was part of our insufficient data, but obviously that was not what was understood by other people, and so that has not been addressed, so that under method of manufacture it still says excess amines are removed by.

But in the first paragraph of what we have it says that the following data are needed: clarification that excess quaternary ammonium compounds, not excess amines, are present during the manufacturing process. It's right there.

DR. EISENMANN: But it was not in the data announcement. It's been added since.

DR. BELSITO: Anyway, the bottom line is we didn't get the answer to that, so how are we going to handle it? Do we say that we presume if they were there they were washed out with the washing? Do we put in a paragraph about N-nitrosamines? Do we say Dan Liebler feels that that was a mistake and we (inaudible) To deal with it at all? I mean, seriously, how do we deal with this?

DR. LIEBLER: Yes, so there are two bases in which I would respond to that. First of all, at the last meeting we didn't know how much of the amino compound, whether it's an ammonium or an amine, how much of that was releasable. We now know that's a very, very small number, so there's no significant release of the organic ammonium component.

If -- I interpret the description of the method of manufacture for the montmorillonite to be either -- well, it says either of two things; neutralizing the acid clay with an appropriate organic base. Now that could be an amine, or by treating the clay with a large excess of the organic salt and water solution.

There they're talking about the ammonium, the organic salt in the water solution. The solution is heated to boiling and then shaken for 30 minutes. The compound is separated by centrifuging and washing with water and alcohol to remove any excess amine if an excess had been used.

The only thing that they talk about an excess -- I mean it's -- they talk about an excess is the organic salt, so I interpret this in its entirety as meaning they make this with -- as they do with the other clay by mixing the clay with a quaternary ammonium compound to bind with the anionic residues in the clay, and that's most consistent with the information that we have about the rest of these. So, if there is any amine used I would infer that there would be a very small amount of it released because we do have data on the quaternary ammonium release that just came to us in Wave 2, and that's shown to be very low.

DR. BELSITO: Okay.

DR. LIEBLER: So that's why I feel that we don't need to go back out and say that it's insufficient for an amine that may not even be used in the synthesis.

DR. KLAASSEN: Safe as used.

DR. BELSITO: So we're not concerned about N-nitroso formation?

DR. KLAASSEN: No.

DR. BELSITO: And that's because there's no amine there, or if there was the way they describe the manufacturing would get rid of it?

DR. KLAASSEN: Right.

DR. BELSITO: Or both.

DR. KLAASSEN: Yes.

DR. BELSITO: Okay.

DR. LIEBLER: Yes. Reference 32, Lillian? You have it available?

MS. BECKER: (inaudible) I should.

DR. LIEBLER: It might be -- if I could look at that, it might be helpful.

DR. BELSITO: And the discussion we need to get rid of the --

DR. LIEBLER: Inhalation.

DR. BELSITO: -- the use of face powder, body dust (inaudible). Well, there are -- I mean it's not two paragraphs because there are spray uses. It was the powder we were concerned about.

DR. BOYER: Right.

DR. BELSITO: So it's just the powder paragraph that we need to delete, right?

DR. BOYER: That's correct, but we would like doing the -- in the context of discussing the powder, potential inhalation to respirable particles.

DR. BELSITO: We're going to do that --

DR. BOYER: Right.

DR. BELSITO: But the paragraph and the discussion of this particular one -- is not used in powders needs to be deleted.

DR. BOYER: Right.

DR. BELSITO: Are you comfortable there, Danny boy?

DR. LIEBLER: I'm still looking at it. I mean you guys -- well, I guess you need to know what I think, huh?

DR. BELSITO: Someone's trying to get in. Oh, they're in. (long pause) Yes, no, maybe?

DR. LIEBLER: I'm on the third page, thank you very much.

DR. BELSITO: You should have taken the Evelyn Wood course.

DR. LIEBLER: So, I'm not sure that this paper is actually a description of the preparation of the ingredient. This is a description of base exchange in montmorillonite and they're using -- they are using amines. They're using a variety of different amines. I don't see any quaternary ammoniums, but I'm not sure that this is the description of the manufacture of the montmorillonite alkonium clay that we're evaluating. This is a study of the exchange of amines -- various amines into this clay, but I'm not sure

that it's necessarily relevant to the ingredient we're studying.

MS. BECKER: And at this point I can't tell you if it's a primary reference that I got from somebody else who is describing the manufacture or not. I do not remember that.

DR. LIEBLER: Because the[y] describe using amines that range from benzanine to paramino dimethyl lanoline, phenylenediamine, even codeine, napthylamine, n-amylamine; lots of things that are not -- certainly not the type of thing that you would put into this clay to give it the properties that this type -- this family of ingredient has.

I think this is a paper that's relevant only to understanding amine exchange chemistry in the clays but not the synthesis of this particular ingredient. It sure doesn't look like it is. I mean it's also, as you mentioned -- it's a very old reference from 1940, so I don't think it helps us, and I don't think it hurts us.

DR. SNYDER: So do they discuss on there about removal of excess amines?

SPEAKER: Says centrifuging and washing with water.

DR. LIEBLER: That's directly taken from the methods -- the general methods description in this paper, but this is just a description of the studies they did with amines in and out of the clays. I don't think that this is a description of the synthesis of the cosmetic ingredient that we're studying.

DR. SNYDER: So we should eliminate that paragraph?

DR. LIEBLER: I think that paragraph is probably not relevant.

DR. BELSITO: So we got rid of difficulty by eliminating paragraphs.

DR. LIEBLER: Process of elimination.

DR. BELSITO: Okay, so we're going to delete under manufacturing -- that is PDF page 17, so that whole -- I like the way you say -- say that word -- montmorilite?

DR. LIEBLER: Montmorillonite.

SPEAKER: It's not the same thing. It sounds like a child's -- children's names because it's so --

DR. BELSITO: Yes.

DR. LIEBLER: I climbed that when I was younger, Montmorillonite.

DR. BELSITO: So we're deleting this whole thing, and then that makes the whole issue of nitrosamines go away, right?

DR. KLAASSEN: Safe as used.

DR. LIEBLER: Right.

DR. BELSITO: So we're deleting it because it's not relevant to cosmetic ingredient?

DR. LIEBLER: Right.

DR. SNYDER: Not relevant to the manufacture of these clays.

DR. LIEBLER: I can see how it came up in the literature search, but it's not a description of the synthesis of an ingredient that we're talking about.

DR. BELSITO: All right. And then --

DR. BERGFELD: Do you have to go to the discussion to make some corrections there?

DR. BELSITO: Yes, well, we have to get rid of the whole powder paragraph.

DR. BERGFELD: Right.

DR. SNYDER: All of that from there on.

DR. BELSITO: And the insufficient data needs we need to get rid of.

DR. SNYDER: And change the conclusion.

DR. BELSITO: And change the conclusion, so this is going as a tentative final safe as used.

DR. GILL: They are making it less restricted, does it go -- does it (inaudible)?

DR. BELSITO: Doesn't it? I mean to give the opportunity for people who might object to its safety to give additional data.

DR. SNYDER: (inaudible) Conclusion.

DR. BELSITO: Yes, we had a conclusion. It was insufficient. The conclusion was it's insufficient for the data --

DR. GILL: Oh, I thought we went out with a data announcement of insufficiency.

SPEAKER: (Inaudible) Data to be insufficient.

DR. BELSITO: Just now.

SPEAKER: In the last 30 seconds.

DR. BELSITO: Right, so this is a tentative final conclusion. I don't know where it was used. It was written like it was a tentative final. It was coming back to us as a final because it had a discussion and a conclusion, but it doesn't matter. The conclusion has changed, and so this will go out as a tentative final (inaudible).

DR. SNYDER: This is listed as a final report.

DR. BELSITO: Right, so we've changed the conclusion. It goes back to tentative final. Okay, so can we have the powder discussion? Leave this?

DR. BOYER: Sure, if you look at the powder paragraph as it appears on the alkonium clay safety assessment report, that's what we came up with tentatively because there was a possible issue for this particular ingredient group that respirable particles could be inhaled from loose powder products, and that for instance if the quaternium could be released from those particulates in the respiratory tract then they might be some issue of sensitization, so we didn't know about that and the panel --

DR. BELSITO: We weren't concerned about sensitization. We were concerned more of an inhaled dust, non-sensitized (inaudible).

DR. BOYER: Yes, I think the issue of sensitization came up with the other team and this team. We discussed possibility of overloading and so on.

DR. BELSITO: Particulate, right.

DR. BOYER: So, we went back to the precedence document, the inhalation person's document, and we actually excerpted in the Wave 2 memo two paragraphs that addressed both of those issues. The likelihood that respirable particulates that are going to come off of a powdered cosmetic product is fairly low because they typically include hydroscopic ingredients so they include oils and so forth. They compact those materials, those cosmetic products, and it's just not the potential for a great deal of release of respirable particles under those circumstances.

What the -- and the other excerpt has to do with the overloading, which in fact occurs only at tremendously high continuous days of exposure to respirable inert dust, for instance, and there's virtually little possibility that that's going to occur from the intentional intended use of a cosmetic product.

What we've received from the Science and Support Committee was some data that reflects the likely exposure to the use of a product containing talc, for instance; a powder product, a loose powder product that represents a conservative scenario in which you would expect the most respirable particle release into the air during use among the various cosmetic types, and through the calculations based on those exposure measurements it is very clear that any exposure to respirable particles, even in that worst-case scenario, is going to be extremely low and very well below occupational standards, for example. So, there seems to be very little risk, and there seems to be very little exposure even under those circumstances, and that's what we're gathering from the exposure papers that we received and from the analysis; the calculations that the Science and Support Committee submitted to us.

And so the question is given what we have written in the precedence document and what we have by way of suggestions to the writers in terms of what would go into this kind of what we're calling a boilerplate -- it's not a report -- are there any changes that we might want to make, any updates based on those calculations, that exercise that the Science and Support Committee submitted, either to the document itself -- the background document itself or to the framework?

If, in fact, we run into another situation like this where we have a loose powder product where an ingredient is present on a very high concentration and there's likely to be at least some

exposure to respirable particles, should we go ahead and develop some verbiage that could be used under those circumstances analogous to the verbiage that we have to address spray products?

DR. BELSITO: So, what you're proposing is then an inhalation boilerplate for powders, for lack of a better word?

DR. BOYER: Right.

DR. BELSITO: And in the Wave 2 what's italicized is what would go into the document itself?

DR. BOYER: That's what's already in the background document, so I just wanted to show you what was already there in the background document. We don't address --

DR. BELSITO: In the background --

DR. BOYER: The --

DR. BERGFELD: Inhalation.

DR. BOYER: The inhalation background paper, the precedence document.

DR. BELSITO: Is pulmonary overload in that?

DR. BOYER: It is.

DR. BELSITO: It is.

DR. BOYER: It has been from the beginning, yes.

DR. BELSITO: All right, so then what you're saying is that the initial respiratory boilerplate that we came up with based upon the back-of-the-napkin calculations assuming talc which would be maybe your loosest powder would still cover the toxicities of a loose powder unless it had immunologic activity.

DR. BOYER: And it may serve as the basis for developing a few sentences that could go into the reports to address the loose powder situation when it's appropriate.

DR. BERGFELD: Would you consider having both -- only making the adaptions that you've just suggested than having one specific to powder in case you didn't need the longer one? Or would you prefer it to be in one document?

DR. BOYER: We would try to keep the -- what goes into the reports very short and we would include that link to the background document for the full explanation, and it would be just something that would be -- we've already got a paragraph that we commonly put into the reports to address the spray -- potential inhalation exposure through spray products, and so this would just be an additional few sentences that would address the situation where it's really loose powders that we're concerned about.

DR. BERGFELD: No brainer.

DR. BELSITO: Okay. Anything else? Because that's going to come up in our next one. We're now going to hexamethylene diisocyanate polymers as used in cosmetics. It's under HDI. So we had gone insufficient at the last meeting asking for stability, sensitization, irritation, and capping and we got all that. We did not get inhalation data, but now we have this powder report that we can put in. The monomer issue was addressed in Wave 2 and we have to add a heavy metal boilerplate, but I thought with all of those we could go safe as used.

Day Two

DR. BERGFELD: …We're moving on to the fourth ingredient, which is clays. Dr. Marks, alkonium clays?

DR. MARKS: In the September meeting the Panel issued a tentative report with insufficient data conclusion. A number of that data was both in this report and then also in our Wave 2, so we felt that at this point we could move forward. And I move that -- or our team moves that we issue a revised tentative report, safe when formulated to be non- irritating.

DR. BERGFELD: It's a motion. Is there a second or a comment?

DR. BELSITO: Second.

DR. BERGFELD: Any comments? Don?

DR. BELSITO: So on PDF page 23, first of all, we've been told that these are no longer used in powders, so that whole paragraph, the second paragraph on that page needs to be deleted.

It appears that there can be heavy metals in these clays, so we need in our discussion to add the usual heavy metal boilerplate.

With the changes in not including the manufacturing of montmorillonite, then it appears we don't need to be concerned about Ron Hill's issue of the free amines. And so that issue goes away.

So I would agree, safe as used when formulated to be non-irritating.

DR. BERGFELD: And are you suggesting that this occur in the discussion that all these be addressed, these questions?

DR. BELSITO: Well, the deletion.

DR. BERGFELD: Deletion.

DR. BELSITO: And, I mean, just the discussion, the only points that I had were heavy metals.

DR. BERGFELD: Okay. Any other -- oh, yeah, Ron Hill?

DR. HILL: Yeah, I did want to make a comment about -- because it wasn't from our team that we requested this ion exchange data that all ion exchange phenomena are heavily affected, really heavily affected, by ionic strength. And so I considered the data we got from industry where they did the study in water, completely nonresponsive to that. It's just that I didn't have the concern in the first place based not on what we had with this specific group of clays, but their high similarity to the hectorites for which we had previous information that, for me, allowed the read across. Lacking that, I would have considered this nonresponsive and we still had gaps and that we were only sufficient in that case on the quat-90 and the stearalkonium. But because of the hectorites data previously, I was comfortable with the conclusion.

DR. BERGFELD: Thank you.

DR. HILL: I thought the data from industry were very helpful. And again, because they did it only in water, I guarantee you, if you study that phenomenon only in water you're not going to get the same answer as you might get in sweat.

DR. LIEBLER: I didn't sweat that. (Laughter)

DR. HILL: Neither did I because we had the other ingredients that I used to read across from the get-go.

DR. BERGFELD: Great. I'm going to call the question. All those in favor of safe, please raise your hands. Thank you. Unanimous.

September, 2015 Transcripts - Alkonium Clays

Dr. Marks' Team

DR. MARKS: Okay. Any other comments? If not, we'll move on to the safety assessment of alkonium clays. So in the June meeting the Panel issued an insufficient data announcement requesting four points which are on Lillian's memo to us dated August 28th, particle size, percent of a cation inolation data ocular irritation. We've received data. Both within following the memo and the report, but also on wave two. We got quaternium-18 bentonite data. One of the questions would be can we read across? Can we include this data in this report? We've got ocular irritation on quaternium-90, and that was okay. So, Ron, Ron, and Tom can we issue a -- we are at the point of issuing a tentative report. The question is what is the conclusion? Our initial conclusion at the last meeting was actually safe, so do we want to go back, particularly with this new data?

DR. SHANK: The only question I had is are the chemists satisfied with the cat ion data? They were concerned about the ration [ratio] of cation to polymer and the stability of that. Could the cation leave the clay? If they're happy with the data, which we have new data on that, than I have no concerns and I think it's safe as used.

DR. SLAGA: I agree. You know, particle size is so large, and we already reviewed ammonium hectorite which was already found to be safe. This is very similar. With all the new data I think we don't have any concerns now and it's safe.

DR. MARKS: Ron Hill, sound good? I think the chemist you're talking about, if I go back and look at the minutes, was that Dan? Dan Liebler.

DR. SHANK: I think both of you.

DR. HILL: No. My concern was not that. I only wanted to make sure that we were comfortable with the lack of inhalation data. Even though we didn't get into inhalation data directly on these we got particle size which is one of the things that I wanted to see and then further information. But I had looked extensively at the previous reports that were very similar ingredients and I was comfortable. The only unresolved issues I had were related to method of manufacturer. There was a bit of sketchy information on the montmorillonite and also the use of an amine in another one. I don't know that we got anything along those lines, but then they're really nothing in all of that that raises such a red flag that I'd argue with a safe conclusion.

DR. MARKS: So you would be in support of me proposing our team suggest a tentative report with a safe conclusion tomorrow?

DR. SLAGA: Yes, sir.

DR. MARKS: Lillian, do you want to mention anything about the quarternium 18 bentonite data? Do we include it? Do we not? You know, you gave us all this data and maybe put it in perspective and then our team can decide?

MS. BECKER: Normally we don't include data that's been in a previous report except if they're in summary. If it's really important. Do you want to add the new data that wasn't there before? And I would expect yes.

DR. MARKS: Yeah. Okay. I want to confirm that with yes.

DR. HILL: Yes.

MS. BECKER: Okay.

DR. MARKS: Okay.

DR. SADRIEH: Can I just? I was just wondering, when we did the review of the data that was provided we thought that there wasn't -- I mean, the levels are 6.5 percent maximum concentration of use, and the data to support this concentration's not available. It's only up to 4.3 percent, so I was just wondering how's that going to be addressed?

DR. MARKS: Rons? Tom?

DR. HILL: I flagged that and I remember we discussed it last time. I think the conclusion was six was not much higher than 4 given the nature of these ingredients, but that may be also that they were waiting to find out anything about any hard data on disassociation propensity for those cations that are "grafted" which really means absorbed strongly. We don't have new data on that, but I wasn't uncomfortable because we have data on very similar clay based ingredients with very similar character in previous reports where we did pretty much have enough to rest our hat on. But that's the best I can do on that. Six is not that much higher than four.

DR. EISENMAN: There was one test, human primary skin irritation test on a foundation at 7.5 percent.

MR. BEST: So basically we find in our notes to the 4.3 versus 6.1. I mean, just as a general as you go through this, obviously, I'm new to this process and I'm very interested in sort of where that line is, you know, how close does the use have to be to the testing that's done just generally? Through this, there are a couple places where it is different, but that was something that kept coming to my mind. Well, how close the data have to be to the general use?

DR. HILL: It does look bad not to have data at 6 percent when the use is at 6 percent. I will say that.

DR. BERGFELD: But you have additional data that was sent to you on wave 2?

DR. HILL: Yes. I didn't feel uncomfortable with any of that, but I got the sense that they were waiting to see what they would get on that because the sensitization is not going to come from the clay. It's going to come from the absorbed constituents were they to dissociate enough to interact with tissue macromolecules.

MS. BECKER: Okay. And I need to -- so here, the human primary skin irritation test at 7.5 the actual amount of our ingredient is 3.19 because apparently it's a mixture, and I missed that when I first ran through this.

DR. MARKS: Yes, I didn't have any safety alerts from irritation and sensitization with these. I think how close do you get to it it's a combination. Again, if it's a mixture --

MS. BECKER: I'm sorry. I'm so sorry. I'm looking at the wrong one. That's for HDI, not this one. I missed it. So when we get to HDI I missed that.

DR. MARKS: But I think also part of it's clinical experience and such, so if there were a number of case reports of sensitivity being reported then I would want to see an HRIPT at the highest concentration used. Also, quaternium-18 bentonite is actually approved by the FDA, so it went through an extensive safety assessment with that including irritation sensitization. It's been in consumer products and no irritation or sensitization alert with that either, so I think that helps with the read across.

Okay. So I'll move tomorrow to issue a tentative report with the conclusion safe. I'll probably confirm with Dan that he's okay with the cation just to bring that up as a discussant point if that sounds, Ron, good to you since --

DR. SHANK: Yes.

DR. MARKS: -- none of us are --

DR. SHANK: I'd like to see if Dr. Liebler's satisfied with the data on cat ion mobility then I think safe as used. Your question about where do you cut off if you have test data at 4 percent but it's used at 6 percent is a very good question. I think it depends very much on the chemical we're considering. If it's something very stable and large, as these are, then the difference between 4 and 6 is probably not important. If it were a single chemical that might penetrate the skin readily it could be very important. In those cases, we usually request test data at use concentrations.

DR. MARKS: Yes. I would suggest the ingredient we just previously had a robust discussion which I recluse myself as an example where we want to actual data as per it penetrates the skin. We know it's a sensitizer.

DR. HILL: I went back to the June report where I was looking and I had made

comment about the uncertainty with the montmorillonite and the amine, and at the end of the process for one of the montmorillonites they -- let's see, where is it? Neutralizing the acid clay with the appropriate organic base, and that would probably be an amine because the rest of the information indicates -- it says, "Centrifuging and washing with water and alcohol to remove any excess amine, if excess had been used." And so in the discussion seemed like we might want to capture any significance of is that excess amine gone. Do we have nitrous amine concerns? That sort of thing. We didn't get any further information on that.

MS. BECKER: Do you want to put that in the discussion?

DR. HILL: I will let you know tomorrow.

MS. BECKER: Okay.

DR. MARKS: Okay. When Wilma asks for discussant points, Ron, you can bring that up if you'd like, Ron Hill. Okay. Any other comments? If not we'll move on to the next ingredient which is siloxanes.

Dr. Belsito's Team

DR. BELSITO: …Okay, Alco conium [alkonium] clays. So at the June meeting we issued an insufficient data announcement for the Alco conium [alkonium] clays. Ingredients were reported a function as dispersing non-surfactant emulsion da, da, da, da. The highest maximum leave on use concentration was 6.5 percent in nail products. They asked for a particle size distribution percentile conium cad ion [alkonium cation] in the ingredient of sedentary cad ion [secondary cation] releasable in the solution, inhalation, and ocular irritation data at maximum concentration of use and I'm assuming we asked for ocular irritation if available.

We got irritation sensitization. We got some Wave 2 data and we got data on Quad-18 Bentonite which I presume we were being asked to read across because we previously looked at this and found that to be safe when we didn't have the same concerns about cad ion [cation] exchanges. Since that's all beyond my level of expertise I will let my colleagues comment on what they thought of the Wave 2 data that we got and whether since now sufficient.

DR. LIEBLER: Well, it's a mixed bag. We do have information on the ranges of cad ion [cation] components in the -- versus the clay material and specifics aren't provided because they're considered proprietary.

DR. BELSITO: They are close to the Quad-18 Bentonite data we already essentially had. So it doesn't really add anything to this report. So Wave 2 is sort of useless.

MS. BECKER: You have most of it but some of the data in there you have not seen before.

DR. BELSITO: So the physical and chemical properties which suggest that the particles are still respirable and that's not been addressed; the inhalation toxicity.

MS. BECKER: For the Quaternium-18 Bentonite, the new data that you have not seen before moved. Sorry, page just changed.

DR. BELSITO: Was acute inhalation and then we got sensitization at 10 percent but we already approved it up to 10 percent.

MS. BECKER: Okay, ocular irritation, allergenicity, acute inhalation, and an Ames test --

DR. BELSITO: Right.

MS. BECKER: -- for an individual.

DR. BELSITO: Brad, I don't know. To me it didn't really seem that the data we got really at --

DR. SNYDER: Yeah, it was a --

DR. BELSITO: -- addressed any of our --

DR. SNYDER: -- Dennis Laba, is he here?

DR. BELSITO: -- needs. What?

DR. LABA: Yes, I'm here.

DR. SNYDER: You were going to provide us some inhalation data last time.

DR. LABA: Yes, I provided to the (inaudible) a list of uses all outside of the U.S. and antiperspirant aerosols. There were about 200 uses and most of them were done with sterile conium bentonite, but all of the botanindian things were also used. But there was no inhalation data that these (inaudible).

DR. SNYDER: Okay, so what -- there was no none (inaudible)? Okay.

DR. ANSELL: But we point out that the exposure is not based on the particle size of the unformulated raw material. The particle size, the inhalation particle size, is driven by the product form. It's controlled in aerosols by the size of the nozzle and it's formulated. So we think that the -- would suggest that the boilerplate are standard inhalation boilerplate that's applicable to these materials as to any of the other materials. Particles of the formulated product is equal to be exposed to it or troubled to be in a -- essentially non-respirable range.

DR. BELSITO: But that would be for error.

DR. SNYDER: There was a lot -- the concern was the powder.

DR. BELSITO: Powders.

DR. SNYDER: Yeah, we were really concerned about the powders but we didn't have anything.

DR. BELSITO: So you're using some face powders.

DR. SNYDER: Face powders.

DR. BELSITO: And up to 2.2 percent.

DR. SNYDER: Right.

DR. BELSITO: So my question is do we need chronic inhalation based upon its use in face powders to 2.2? And then I also said do we need to relook at the other clays we reviewed for aerosol use if we're concerned about these.

DR. SNYDER: So how do we deal with it in (inaudible) report? Do we know?

DR. BELSITO: I can't get on the Internet here so I can't look at other reports.

MS. BECKER: So it's safe as used.

DR. BELSITO: But did we have powders? Is anyone else able to get on the Internet from this room?

SPEAKER: Yeah, I'm able to connect with -- to Doubletree.

DR. BELSITO: I didn't even get that offered to me.

SPEAKER: Yeah.

DR. BELSITO: In my room I have it.

DR. FIUME: It doesn't come up asking for a password so it's connecting automatically.

DR. BELSITO: Which one?

DR. FIUME: Doubletree should connect automatically.

DR. LIEBLER: I can't see Doubletree here. It's --

DR. BELSITO: I'm not getting Doubletree. Other network maybe. I still can't get on so I can't look at the report but (TRACK 307 inaudible).

MS. BECKER: Okay, the (inaudible) was used at two percent in powders and nothing else was.

DR. SNYDER: Then how did we -- in the discussion how did we deal with those inhalation issues?

MS. BECKER: I don't see anything about inhalation (inaudible). No we did not mention inhalation of powder.

DR. BELSITO: What was the particle size information we added to that?

MS. BECKER: Paging up. Because of aggregation the effected particle size will be larger and the surface area will be considerably smaller than the actual particle size of the aggregate surface area. During the growth of (inaudible) spike in the transformation or the (inaudible) supposed to become interlocked and become difficult to separate after strong sharing [shearing] forces, except by strong sharing [shearing] forces. Differences in the effect of particle size affect (inaudible) are extremely important in the termination of properties such as ion exchange, the viscosity, and fluid loss.

DR. SNYDER: Well we have physical and chemical properties that say that 20 to 58 percent are less than 10 microns. And it was the basis for us asking for that data.

DR. BELSITO: That's fine. Then we'll (inaudible). So what do we do with this (inaudible)?

DR. SNYDER: So we were previously in submission for particle size percent composition by weight, cad ion [cation], inhalation data, concentration of use, and ocular irritation.

DR. BELSITO: It sounds like we're still insufficient with some (inaudible).

DR. SNYDER: We got some particle size data and we got some ocular irritation, but we didn't get any of the percent rate; cad ion [cation] content and inhalation data.

DR. LIEBLER: We got a range for one product but we didn't get any information on the releasability of the cad ion [cation] and this is the thing that concerns me the most. In other words, for a given amount of this Alco conium [alkonium] clay, how much of the Quaternium-90, for example, is releasable? And this is of concern to me. It's completely (inaudible) in the description of the method of manufacture. On PDF 21 it says that these exchanges typically performed by addition of the appropriate aconitum [alkonium] chloride to an alcohol water slurry of the clay. And I made that suggestion, this exchange occurs under mild conditions. And, you know, an alcohol water mix wouldn't be that different from the formulation that this material would be in the finished product. So that's why I think it's a relevant question to ask about the releaseability of the cad ion [cation] component. We don't have any response to that question but we have a range of, you know, composition by weight provided in the Wave 2 response with the explanation that it's proprietary. So it's a very broad range. Still nothing on how you release to this.

DR. BELSITO: Or chronic respiratory.

DR. LIEBLER: Yeah, so that's -- that was my concern; more of a chemical issue, but I think since the Quaternium-90 compound, we don't have any information on that. That one has 64 uses, up to six percent. Obviously the stearalkonium bentonite is the one that is the major driver of this report. Four hundred and twenty-three uses up to six and a half percent also.

DR. BELSITO: So our insufficient needs really haven't changed.

DR. LIEBLER: Not much.

DR. BELSITO: So this goes out as a tentative, final, insufficient for pretty much everything we asked for before.

DR. LIEBLER: Right.

MS. BECKER: Okay.

DR. BELSITO: Okay, so insufficient for the same data needs. The little bit of data that we got on cad ion [cation] exchange, did that eliminate the need for --

DR. LIEBLER: There wasn't any data cad ion [cation] exchange. There was just data on cad ion [cation] percent.

DR. BELSITO: Okay, okay. So insufficient for all the same data needs.

DR. ANSELL: All right, so we did provide inhalation data on the Quad-18 Bentonite in Wave 2.

DR. SNYDER: Yeah, there was a -- nothing used in a face powder but as a cream foundation.

DR. ANSELL: Right --

DR. SNYDER: Yeah.
DR. ANSELL: -- and that's not used to, you know --
DR. SNYDER: Yeah, powder.
DR. ANSELL: -- the powder.
DR. SNYDER: Yeah.
DR. ANSELL: It's used in a --
DR. SNYDER: Face cream.
DR. ANSELL: -- face cream.
DR. LIEBLER: So Quad-18 and Quad-90 are as I pointed out fairly similar in structure. So I would be even happy if we got -- release -- releasable cad ion [cation] data from Quad-18. But what I'd really like most is Quad-90. But if it was a very, very small fraction from Quad-18 than I -- I think my concern would be pretty well satisfied.
DR. BELSITO: What this Quad-90 data needs are your main concern.
DR. LIEBLER: Correct.
DR. BELSITO: So a tentative trial --
DR. LIEBLER: (inaudible)
DR. BELSITO: -- would be [in]sufficient for all the same data needs.
DR. ANSELL: Even for the inhalation.
DR. BELSITO: Yes.
DR. ANSELL: Because the 18 is not relevant; it's inhalation data?
DR. BELSITO: We only have acute inhalation for 18, right? We have four hour exposure. I don't think that's relevant to consumer use. Acute inhalation, Wave 2, 5.7 milligrams per liter for four hours was negative in 10 animals. That doesn't really help here and this doesn't help me.
MS. BECKER: What about the question of including the Quaternium-18 Bentonite data that was not referred to before?
DR. SNYDER: For a read across?
MS. BECKER: For a read across.
DR. LIEBLER: It's okay if it doesn't solve our data needs --
MS. BECKER: But the --
DR. LIEBLER: -- but it's okay to include.
MS. BECKER: Okay, good. Thank you.
DR. BELSITO: So tentative, final, insufficient for all the same data needs and include the Q-18 Bentonite data from the prior report. Include summaries.
DR. LIEBLER: Yeah, but it's not quite all the same data needs. The one data need that they did satisfy was the percent of alco cad ion [alkonium cation] in the preview.
DR. BELSITO: But not the releasability.
DR. LIEBLER: But not the releasability.
MS. BECKER: So we don't need information on the ratio.
DR. LIEBLER: No.
MS. BECKER: We knocked one thing off the list.

Day Two

DR. BERGFELD: ... Moving on to the third ingredient in this category, the alkonium clays. Dr. Marks?
DR. MARKS: So, in the June meeting we issued an insufficient data announcement for these alkonium clays that are listed in Lillian's memo: Particle size, inhalation, alkonium cation, inhalation data, inocular [and ocular] irritation. We largely received these, so we felt that we could issue a tentative report with a conclusion of safe, but our team wanted to confirm with Dan that he

thought the the alkonium cation data need was met.

DR. BELSITO: Oh. Do you want Dan to respond first, or me?

DR. MARKS [DR. LIEBLER?]: So, I didn't. I'd be a Wave 2 submission and describe the ranges for the approximate loading. And just to reiterate, the reason I had this concern about the release of all cation component was because in the description of the loading process where they take the clay and they load it with the cation of interest, this is done as described in our text in (inaudible) water suspensions. And that seems to me to be sort of mild conditions. It's not -- no extremes of pH or salt characteristics or anything like that, and that led me to ask the question of whether or not under similarly mild conditions the cation can be released. And that was the main reason that point was articulated. And I thought it was particularly important, because quaternium-90 is in this and we don't have a review on quaternium-90. So, we would like to be able to know whether or not -- you know, the cation itself becomes essentially an impurity in the intended product. So, I didn't see that in the Wave 2, and I think that kind of information should be gettable by industry, and I suspect that if the cation was very readily, easily released it would be unsuitable product formulation anyway. But we need data, I think, to support that, so I'm sort of sticking by my feeling that we need those data to support this.

DR. MARKS: So, I withdraw my motion.

DR. BELSITO: So, we're sort of dismayed by the fact that the data in Wave 2 was a little unclear, because it was on Q-18 bentonite, which is actually a product we already reviewed. It wasn't -- it's not a product that we're looking at now. There's a Q-18 bentonite something else that we're looking at now, but it's not Q-18 bentonite. So, we were insufficient, as Dan said, for all the same data needs except for the percent cation but not for the amount that is releasable in formulation. And we thought that it might be helpful to get the new information we got on Q-18 bentonite and all of the prior information on Q-18 bentonite that we reviewed and to bring it in.

We also continue to be concerned particularly, Paul, about the fact that these are used up to 2.2 percent in powders and that this -- facial powders -- and that the size that we've been given is in fact restorable. And we have just an acute toxicity study on Q-18 bentonite, not on any of these products, and while we realize that it's probably a product particulate effect, we have no chronic respiratory on inhalation of particles of this size. We don't think they need to be on the materials themselves, because we thought they would be fairly inert, assuming we get some data about cation exchange coming out of them, which we don't have, and assuming that there isn't a high cation exchange, and we'd be just interest in what happens when you breathe chronically particles of a size of these materials in a facial powder.

So, we were insufficient for information about cation exchange and about some more chronic -- it doesn't have to be 300 days but more than a 4-hour simple breathing test on Q-18 bentonite.

Let me see if there are any other issues that we're insufficient on.

Paul, can you help me out here?

DR. SNYDER: Yup, that's it.

DR. BELSITO: That was it.

DR. LANGE: Just to clarify, we're not aware it's used in any powders. It wasn't a powder product actually that was in the report.

DR. BELSITO: It says "powder."

DR. SNYDER: It says "face powder."

DR. SNYDER: Is that a pressed powder? That's one of the lipid --

DR. EISENMANN: I later did some additional information that that's not a powder. I went back to the company, and they said that was an error, that it's not a powder product, that it's a liquid foundation containing that.

DR. BELSITO: Okay, well, we still need cation exchange, so could you please

provide us with that correct data at the next meeting?

DR. MARKS: Yes, sir. So, does that mean that chronic inhalation is not an issue at this point?

DR. BELSITO: It will go away if this is in fact correct. But, you know, let's get the data. At this point, we've been -- this document says it's a face powder until we're told by industry it's not. Maybe in the future industry will get their act together or report things correctly.

MS. BECKER: Believe it's in Wave 2.

DR. MARKS: How about sprays? Is that -- it's not --

DR. BELSITO: Sprays are going to be controlled by the nozzle size and not by the particle size.

MS. BECKER: So, I don't --

DR. MARKS: Then you're saying, Lillian, it has --

MS. BECKER: I'm double checking right now.

DR. MARKS: So, if it's in Wave 2 we'll assume it's not in a powder. If it's confirmed in Wave 2 we can eliminate that insufficient right now.

DR. BELSITO: Right.

DR. MARKS: So, we'd move for an insufficient conclusion. We need the cation exchange and -- is it there? Updated -- remove -- face powder is not a powder, it is a cream formulation. It's actually in Wave 2. Lillian has it in there. We missed that.

DR. BELSITO: Okay.

DR. MARKS: So, I think at this point it's just cation exchange we need.

DR. BELSITO: But it's still listed in the document as a face powder, so that needs to be removed.

DR. MARKS: Yeah, exactly. And that will be removed, okay?

DR. BERGFELD: Ron Hill has a statement.

DR. HILL: Yes, I do. We won't have a statement in the document indicating that they shouldn't be used without further supporting data on inhaled products, because -- we will not have, because we won't have an inhalation use for inhalation exposure.

DR. BELSITO: Well, we will from a spray.

DR. MARKS: Spray, yeah.

DR. BELSITO: Okay, we have that boilerplate.

DR. MARKS: All right, and I think that should be -- since it's such an important point -- that should be captured in the discussion: Why the spray's okay; why we were concerned about fragrance; in the future if somebody wanted to formulate a powder containing these ingredients, that we have concerns about that. It's not the use now, but in the future.

DR. BERGFELD: So -- Ron Hill again?

DR. HILL: Yeah, one more, and I think this is directly related to Dan Liebler's concern. In the last sentence of the montmorillonite -- and this was the method of manufacture -- it says, "The compound is separated by centrifuging and washing with water and alcohol to remove any excess amine if an excess had been used." I think when they say "amine," they're meaning quaternary ammonium compound, but I'm not certain of that, and we didn't get any more data on that, and I would like that clarified because if it is amine, then there might be excess amine there and we'd worry about at least a nitro amine issue.

DR. LIEBLER: It strikes me as probably just a little imprecise.

DR. HILL: I think that's the case, but I would like to know that for sure.

DR. BERGFELD: All right. Well, we have a motion. We had a motion. It was removed. We have a new motion. Do we have a second? Can you restate your motion?

DR. BELSITO: My motion at this point is for cation exchange in the product and clarification from industry that in fact it is not used in face powders.

DR. MARKS: So, that would be moving for a tentative report with that conclusion, insufficient --

DR. BELSITO: Insufficient for those data now.

DR. BERGFELD: And you're seconding that?

DR. MARKS: Yes.

DR. BERGFELD: All right, any further discussion? Seeing none, call the question. All those in favor of this conclusion.

GROUP: Yes.

DR. BERGFELD: Thank you. Unanimous.

Transcripts – Alkonium Clays
June, 2015

Dr. Belsito's Team

DR. BELSITO: Okay, clays. Okay, so this is the first time we're looking at it. Eight ingredients. Highest leave on concentration 6.7 in an L-product. Basically the datas on sterileconium [stearalkonium] bentonite and where do we go. I guess the first question I had for my teammates is if we don't expect these to be absorbed or do we and if they are not absorbed can we go safe as used?

DR. LIEBLER: Yes.

DR. BELSITO: Okay, then the question I had was the alkonium [alkonium] cations since we know that can be potentially irritated how tightly bound are they? I'm looking at page 9 of the PDF how tightly bound and are they likely to be released? Because on page 10 it says these cations can easily be exchanged which to me suggested they are not tightly bound. Says "the cations can be easily exchange because they are not retained in the middle structure by electrostatic attractions. Whatever that means.

DR. LIEBLER: I'm looking for the exact language you were pointing to Don, you are on page PDF 10?

DR. BELSITO: Page 10, the last sentence.

DR. LIEBLER: Okay, last sentence or the first paragraph?

DR. BELSITO: Correct.

DR. LIEBLER: So here's how I interpreted that. Those cations can be exchanged under conditions that are conducive to the exchange. In other words during manufacturing modification processes or extraction. What I don't know -- these can be exchanged under conditions that are chemistry conditions -- necessarily perhaps as distinct from use conditions, but I don't think we have any data to indicate under conditions where these might be formulated in a cosmetic product, how readily or how easily the cation components can be leached out or exchanged out. My hunch is that they would be pretty stable but that's not data that's a hunch.

DR. KLAASEN: I agree with Dan that's what I think would happen also and that's the way I interpreted it, but I think we really need to go back and ask for some specific -- this is biological exchangeable in our bodies or is this just during the production?

DR. BELSITO: Because they used the highest concentration of quaternium-90 bentonite 6.1 in the eye area and then we have 2.5 for sterile conium [stearalkonium] bentonite in an eye area, so if these quaternary compounds can get out, they could irritate and we have --

DR. SNYDER: I had a question about under physical/chemical properties it says that we have 30 percent or less than 10 microns and we do have an inhalation use? Particle sizes reported to be less than 10 microns 30 percent?

MS. BECKER: Yes.

DR. SNYDER: Or is it bentonite?

DR. LIEBLER: Are you waiting for an answer?

DR. SNYDER: Yes.

DR. BELSITO: Well, I mean I think the biggest issue is that we don't have ocular irritation, right?

DR. SNYDER: Yeah, we have it on the bentonite.

DR. BELSITO: Repeated dose.

MS. BECKER: Thirteen on the PDF?

DR. BELSITO: Yeah, we have that. That is was severely irritating and then we have that at less than 1.25 percent for this so for this so we have severely irritating at 100 percent and we have 31 to 31 milligrams and 0.1 ML [mL] vehicle nonspecified with slightly irritating and it's used at

2.5 percent in an eye right? And then we have individual and that's why I was asking about the release of these quaternary compounds because we have the sterile conium as an ocular irritant as well. I mean --

DR. ANSELL: It's an interesting -- a worthwhile question to ask but considering the material is nonirritating topically and non-sensitizing and it's a solid it is likely that those irritations weren't abrasive and due to the form not necessarily the chemistry.

DR. BELSITO: I mean I'm just raising these issues to we feel that that's okay or do we want to say insufficient mass for ocular toxicity available at concentration of use or do we want to use a caveat when formulating to be nonirritating which we've done for other issues that can be irritating. What we are told is that the cations can leach out? We don't think that's going to happen, it would be a manufacturing process that would do that, not a cosmetic use but that's only a guess not a fact is what I would say.

DR. LIEBLER: We have under the impurities section on PDF page 11 as noted above -- I'm just reading the current text -- it says, "As noted above these ingredients have high caton exchange capacity. Depending on the composition of a given cosmetic formulation the degree to which these alkonium salts may be exchanged out of the end ingredients will vary accordingly there may be some result in free alkonium salts. That's sort of more discussion language which it's a reasonable supposition but there's no data to support that. I think we ought to see if we can get some data on this question. On the stability and in -- not solutions but in suspensions of neutral PH or under conditions comparable to formulation in a cosmetic product which will be mostly neutral PH I think. What is known about the stability of these with respect to releasing alkonium salts? I'm sure small amounts might be released but if you look in the method of manufacturer paragraph right above the impurities it talks about making the salts from montmorillonite and you either treat it with the appropriate organic base that's very synthetic kind of conditions or by treating the clay with a large excess of the organic salt in a water solution.

Again sort of synthetic conditions, so I expect these things are really quite stable after they are initially produced. You wash away the excess reactants and the you have something and it's reasonably safe. But it would be great if we had some data to support that. Just a representative data, but as opposed to our reasonable supposition because otherwise we would need to take these impurities language for example and make that part of a discussion that would talk about what we know about how these are manufactured and what their likely stability would be. We can even just point to the fact that these are held in place by electrostatic interactions which aside from covalent bonds are the strongest chemical interactions around.

This is not even -- stronger even than hydrogen bonding, so it's pretty strong.

DR. SNYDER: And then going back to the inhalation issue the boiler plate that we have for aerosol sprays isn't applicable to powders and we have powder use here. And we know that they have sizes in the respirable sizes so I think we are going to have some inhalation data.

DR. BELSITO: We're going insufficient for stability and cosmetic formulation in terms of release of the cations. Inhalation data. Do we want to ask for ocular irritation if available at concentration of us?

DR. KLAASEN: Why not?

MS. WEINTRAUB: What about the fact that there is really information about one chemical and not the seven? And I know the suppressed is broader, but do you think it makes sense to specifically ask about information regarding the other seven ingredients?

DR. BELSITO: Well the one that would worry me the most in terms of what I do is the stearoyl alkonium and we've got data on that. I don't know Dan, Walt and Kurt in terms of the other components of these clays?

DR. LIEBLER: We have no data. None of these compounds really serves as a read across. I think read across doesn't apply to inorganics basically. And I think stearoyl alkonium

bentonite is the most extensively used.

MS. WEINTRAUB: So does that mean you are saying that you don't think the other ingredients should be included here?

DR. LIEBLER: I'm thinking.

MS. WEINTRAUB: Okay.

DR. KATZ: I was going to ask a similar question. With their being included you need data from all of the or enough data to be able to say now they are not used in great quantities that they are safe to be used.

DR. LIEBLER: I think with the clays -- the clays per se aren't really going to be the issue. They are large carriers. They are derivitized with these alkoniums and that gives them this kind of greasy lipophilic character, but the consequence is we are really concerned about the alkoniums that are on the clays. In that case can we go back to our data on the alkoniums and use that as a framework for looking at these?

MS. BECKER: Page 16.

DR. LIEBLER: Yeah, I'm just looking at the table on PDF 5. So, Lillian refresh my memory the hectorite is a similar framework?

MS. BECKER: Yes, it is and in fact it was just lifted right out of the report.

DR. LIEBLER: Okay, I thought it looked familiar. Of course, it means I actually reviewed that report too. A nice thing about the hectorite reports is that we have pretty high concentrations of use, they are quaternium 18's, stearalkonium, yeah.

DR. SNYDER: So we can or cannot read across?

DR. LIEBLER: I think the term "read across" should be limited to organics where there is a systematic variation of structure. We can draw reasonable inference from these other reviewed ingredients where we have more consistent -- or if we have more test data. These are similar to the clays in that they can release the cations and we have at least from table 2 on the PDF 16 that single dose cutox repeat a dose genal tox irritation sensitization oculate earlier irritation. That's with the hectorites. And then with the quaterniums themselves -- the quaterniums 18's and quaternium bentonite which was already reviewed we'd have single does tox, repeat a dose tox, irritation, sensitization, ocular irritation and phototox. The only possible flaw in using these as analogues for evaluation safety is the assumption that the release of the alkonium piece would be similar to the release of the alkonium piece from the clays that we are now reviewing. That's the assumption.

DR. GILL: Right.

DR. LIEBLER: I think it's reasonable but I'd like to know more about the stability of these things.

MS. BECKER: Does page 18 the alkonium chloride information and the (inaudible) turn the page down.

DR. LIEBLER: Right, so it depends on alkonium chloride sterile, alkonium chloride. Don can perhaps answer that.

DR. BELSITO: Does that help in terms of what?

DR. LIEBLER: Your comfort level with the data in this report.

DR. BELSITO: Again I mean I raised that issue. They are of concern to me because of the irritating capabilities and therefore in a high use around the eye of 2.5 percent sterile iconium [alkonium] clay either warrants some ocular toxicity if available or some idea of how tightly bound those are because you see that benzalkonium chloride and sterile alkonium chloride are ocular irritants and they sterile alkonium chloride ocular irritation concentrates as 1.25 percent and those were slightly intransiently irritating and we have it at 2.5 in an eye product.

DR. LIEBLER: The 2.5 percent is for the stearayl alkonium bentonite.

DR. BELSITO: Right.

DR. LIEBLER: And that's probably a whole lot of bentonite and a little bit of stearoyl alkonium based on the structures.

DR. BELSITO: Yeah.

DR. LIEBLER: So, it would be nice to know approximately how much stearoyl alkonium would actually be -- the equivalents would be present in a 2.5 stearoyl alkonium bentonite application.

DR. BELSITO: That would help too.

DR. LIEBLER: Yeah, because that might help...

DR. BELSITO: Right. At least it would be low irritation by ocular irritation. That's fine too.

DR. LIEBLER: That's probably not a calculation we can do here at the table but it might be possible to come up with that number. If it's a 50 fold dilution or more then I think our level of concern is going to go way, way down. Fifty fold is not necessarily a magic number here but you get my point.

MS. WEINTRAUB: Also, in looking at the March 2015 SLR that was posted there is other information that was requested too that hasn't been received such as no carcinogenicity data and other things, I don't know if it makes sense to revisit that list and see.

DR. BELSITO: I think that is a generic list -- we -- the Panel hasn't looked at it.

MS. WEINTRAUB: Okay.

DR. BELSITO: It's just a generic list going out and I think that we're dismissing the systemic portions of this because we don't think the molecules are going to be absorbed.

MS. WEINTRAUB: Right.

DR. BELSITO: Or at least as they clay, so we're past that, we're looking more at just simple -- simply skin issues that was the first question I raised. Are we concerned about absorption and if not then let's look at the skin.

MS. WEINTRAUB: Okay.

DR. LIEBLER: And inhalation.

DR. BELSITO: And inhalation and ocular, right?

DR. LIEBLER: Yeah.

DR. BELSITO: That's where I have right now for these ingredients is insufficient, some idea of the stability and formulation of these cations or an off the cuff calculation that shows me that the amount of stear alkonium and benzalkonium is below the irritant threshold for those alkonium chlorides. And then some inhalation toxicity because they are used in powder and the information we have is that those sizes can potentially be respirable and then beyond that we're comfortable because the size of the molecules precludes concern for systemic toxicity due to lack of absorption.

DR. LIEBLER: So Lillian maybe the way to ask the question about this is what is the percent base alkonium equivalent by weight in these? Can we get a range for that? Yeah, percent by weight and if they have it percent releasable by weight.

DR. BELSITO: Okay, anything else? Okay, so it's 12:05, I suggest we break for lunch and maybe resume at 1:00.

Dr. Marks' Team

DR. MARKS: Thank you. Thanks. Thanks, that's always helpful. Let me see. The next one: alkonium clays, let me pull that up. This is the first time we've seen these eight clay ingredients, and then -- Tom, Ron, are the ingredients fine, and the grouping and then are there any needs?

DR. SHANK: I think we need to hear from the chemists, we need, or I need two

assurances, one is that clays will not penetrate the epidermis. Then for systemic toxicity, is not needed. I didn't see that in the report. The second one --

SPEAKER: Where did you get that (inaudible, off mic).

DR. SHANK: -- stearalkonium bentonite can be used for read across, do the chemists agree with that? Do the chemists agree that can use stearalkonium bentonite to read across from safety of the other clays?

DR. MARKS: So when you say the chemist, who?

SPEAKER: Check that out.

DR. SHANK: Well, that would be Dr. Hill and Dr. Lieberth, and Dr. Heldreth.

DR. MARKS: Mm-hmm. And we only have -- we have Ron though. So, the first question, do clays penetrate the skin? And if yes -- yes?

DR. SHANK: If yes, then we need more data.

DR. MARKS: More systemic --

DR. SHANK: If no, then we can betonite as the read across, then they are safe as used, two ways.

DR. MARKS: And the second was the --

DR. SHANK: The stearalkonium bentonite, can that be used for read across? If it can, and these don't penetrate the skin so you don't need systemic data.

DR. SLAGA: Do you want to penetrate?

DR. BERGFELD: You might want to just look at this --

DR. SHANK: As it tries to stick, and you cannot - -

DR. MARKS: Ha-ha. Do you know?

MS. BAKER: Yes. I went and looked at the discussion for the other reports that included this on page of the PDF. That talks about dermal penetration and for the hectorites.

DR. SHANK: Twenty-nine?

MS. BECKER: Page 29.

DR. HILL: I was looking at the bottom of page 28, I have a number of sections flagged about the previous testing, because that's -- I relied on the hectorite information heavily, and I don't know if I flagged the language on --

DR. MARKS: Oh. So there you --

MS. BECKER: It sounds like (inaudible) across list.

DR. HILL: Because the clays themselves, as far as I can see, presented no issue. So, the only issue was, do any of these alkonian compounds dissociate appreciably because the problem with language that's graft for which I have a terrible problem with that word, is grafting suggest to me covalent bonding, and it's not. But then they are very strongly absorbed. Or actually in some cases absorbed and absorbed, and don't seem to dissociate, don't seem to desensitize, and I pretty much read everything across from previous work on the hectorites, and decided all was well.

That was way I viewed the whole report. So I did -- That's my take on it, is since we haven't been seeing sensitization monomer, other clays that have been on the market for a long time. You didn't see in the case reports some data given?

DR. MARKS: Well, and we have the stearalkonium, this is what Ron is talking about, the read across, not sensitization when applied.

DR. HILL: Well, it wouldn't necessarily be 100 percent read across because the cross is not necessarily the same, except that --

DR. MARKS: And I -- I'm not aware of sensitization.

DR. HILL: So, it was the pass work on the hectorites that -- and the experience with them, for me, it said that the read across was okay.

DR. MARKS: Ron Shank, what do you feel about that? Do you still want to -- So, you've got -- So do you take -- do clays penetrate the skin? And you felt the hectorites read across

from the previous with the answer, answer to that?

DR. HILL: And let just jump back --

DR. SHANK: On the bentonite, we have bentonite in this report.

DR. HILL: Let me just jump back one place though, is that I did focus heavily on inhalation because we don't have data on that. I didn't find anything I felt comfortable relying on. So I wasn't sure that we can conclude safety for the ones that could potentially be inhaled without something to rest it on.

So I wrote, needs particle size characterization for all the ingredients. And I wasn't worried about getting down into the lung so much as potential for something happening in major mucosa, for example, and upper respiratory, potentially.

DR. MARKS: So, if we don't have a particle size with the inhalation, will boilerplate still answer that?

MS. BAKER: It's pointing at the other group, that the inhalation has to do with the reports about the powders, and most of the uses of these are powders.

DR. MARKS: Pardon?

DR. HILL: Face powders.

DR. MARKS: The inhalation?

DR. HILL: Yes.

MS. BAKER: Yes. If you'll look at the -- yes, if you look on 20, most of the uses that are engrossed in their powders are not expressed.

DR. HILL: So, I wasn't concerned about systemic toxicity at any level, just what might happen with heavy exposure, and nasal mucosa; more about the clays that alkoniums. If there hasn't been anything showing up-to-date on this inhale hectorites, aren't there? Some only use hectorites? That was the question I could -- I'm not sure I've tracked that down yet.

MS. BECKER: That's page 27 on the PDF.

DR. HILL: I'm on it.

DR. MARKS: Yes. I'm here.

DR. HILL: Incidental inhalation sprays up to 2 percent for disteardimonium hectorite and if this was a big problem, by it would have pushed on up.

DR. MARKS: So, Ron. You know, you are like using the previous hectorite report to substantiate the safety and beats the clay ingredients.

DR. HILL: In combination with the data we have on that.

DR. MARKS: Yes. Ron Shank, does that now make you feel more comfortable?

DR. SHANK: It does.

DR. MARKS: So, should we move forward with a tentative report, safe, for these clays?

DR. SHANK: Yes.

DR. MARKS: Tom, do you feel the same?

DR. SLAGA: Yes.

DR. MARKS: And Ron Hill?

DR. HILL: Yes. Sorry.

DR. MARKS: No. That's okay. Do we -- you know, to me it's self-evident, right, to sort of raise this question; it's not surprising if you put clay on the eye it's very irritating. And that's obviously under --

DR. SLAGA: If you put anything in your eye it's irritating.

DR. MARKS: Yes. So, I think it's used for eyeliner or mascara.

MS. BAKER: Yes.

DR. MARKS: Let me look at the use now.

MS. BAKER: It's 33 on the PDF; eyeliner, eye- shadow, eyebrow pencil, eye lotion,

mascara, face powder.

DR. MARKS: Yes. So should we handle that in the discussion? Just a note, that as used in the personal care products used near the eye, and because it's very irritating at 100 percent -- one shouldn't (inaudible).

SPEAKER: 100 percent?

DR. MARKS: Exactly. Or should we just ignore that?

DR. BERGFELD: I wonder why they mentioned that, 100 percent versus 0.00.

DR. MARKS: Okay.

MS. BAKER: And the highest is 2.5 percent, and you have the -- you have 100 percent, you also have 1-point- something.

DR. MARKS: So, team, just leave the report as is, and don't even point out the eye, even though it's used in personal care products around the eye? It's obvious that you don't put clay in the eyes.

DR. SLAGA: Even with most products you (inaudible, off mic).

DR. MARKS: Right. Exactly.

MS. BECKER: We have stearalkonium bentonite, 31 to milligrams, and 0.1- they are saying, of what, and that came out as slightly moderate use.

DR. MARKS: Okay. Yes?

MR. LABA: could I? Dennis Laba. I just wanted to bring up, in case it comes tomorrow about the inhalation, these quaternized clays have been used in antiperspirant aerosols for over 30 years, as the suspending agent there so,

MR. HILL: Well, I now I can't walk into the room, when somebody is using an antiperspirant aerosol. But, yes, the point is it's a long history.

DR. MARKS: So, because that issue came up, then are we going to have, can you supply some sort of document that suggested safely been used in this fashion, and are either no-case reports or no series?

MR. LABA: I'll (inaudible). You know, all kinds of -- it's on the label. They are all on the label of antiperspirant aerosols.

MS. BECKER: But they -- how long you could in there has not used -- like if you can just write us a memo.

MR. LABA: Yes. I can do that.

DR. MARKS: That's what I'm trying to do. You are giving us an anecdote of these are safe because they've been used on aerosol deodorants for 30 years, presumably the second part of that, there have been no significant reports of inhalation toxicity, with that use. So I would want to have both sides of that.

MR. LABA: That we'll check, and we'll check with them.

DR. EISENMANN: For these specific ones, on the deodorant we didn't get any uses, so maybe it's the hectorites here? Is that right?

MR. LABA: The hectorites, but I know bentonites have also been used.

DR. EISENMANN: Because I mean, for the ones listed there, no deodorant uses reported for either VCRP or us.

DR. STEINBERG: They are an antiperspirants.

DR. EISENMANN: Oh. They are anti -- oh, that's right. Okay. That's that drug, so it's like -- Okay.

MR. LABA: Mm-hmm. True. True. Sorry.

DR. DEWAN: I was going to say that, it's -- to bring confusion here.

DR. HILL: Or it should in a sense they are drugs we probably should be able to find information than --

DR. MARKS: Good. And your name again, so we get it?

MR. LABA: Dennis Laba.

DR. MARKS: And where?

MR. LABA: With Presperse, but I used to be Elementis who made those products

DR. MARKS: Okay. Good. Thank you for any other questions. Thanks for that comment.

MR. LABA: Yes.

DR. MARKS: Ron, do you have -- Ron Hill, because you brought up that issue?

DR. HILL: Not a question for him at all, but it relates to -- I had two comments on here, one is that we don't have any information about the method of manufacture on the cebollites and bentonites, and given the uncertainties with respect to montmorillonites, I'm going to have to find what that uncertainty was that I mentioned that wants the -- something for it. But anyway, I don't invest in insufficiency.

The other question I have in relation to read across in particular was, on your impurities section on page 11, it says, depending on the composition of a given cosmetic formulation with the degree to which these are alkonium salts may be exchanged out of these ingredients there. Accordingly, there may be some resultant free alkonium salts. There's no reference given. And do we know where that information came from because --

MS. BAKER: Bart.

DR. HILL: Okay. So, I mean if -- yes, hypothetically he was sounding like me for a moment I guess, but I was wondering do we have information to suggest that that would in fact occur under conditions of use, which I rather doubt, because if it did, we might need sensitization because people sensitize to these quaternaries. They won't die from that, just be all red and itchy, and blotchy.

DR. MARKS: So, I did actually work with quaternium 18 that night, and so, as a prevention of allergic contact, dermatitis to poison ivy, and it actually was approved by the FDA, so there's a lot of data there. There's no report that I wanted to -- 19 bentonite. I have that reference here

DR. HILL: So, if we have no data to suggest that these do in fat exchange off of clays where they are very strongly absorbed then that's just the hypothetical, it's a hypothesis that it could happen, and we might need to be at least more careful about how it's stated.

MS. BECKER: Yes. Just the morning, we are still in there.

DR. HILL: Yes.

DR. MARKS: Possibly we could just take it out.

DR. HILL: it would be nice to have -- as usual it would be nice to have information that it doesn't happen. As in, somebody has actually studied this and knows it, I would have -- I would be surprised if the FDA approved of -- those without at least investigating that possibility. So can we look, -- I mean, I'm sure I should have looked a little more thoroughly before now, and didn't.

MS. BECKER: Exactly, what are we checking for again, the FDA?

DR. HILL: And let's see what we could find.

MS. BAKER: Exactly what are we --

DR. HILL: It hasn't been studied, and we know it's really not releasable once it's in there.

MS. BECKER: Ah. That's not --

DR. HILL: Alkonium salts, at least from the clays, once they are in there.

DR. MARKS: Okay. So, tomorrow, I will be moving the alkonium clays, then issued a tentative report, with a safe conclusion. Okay.

DR. HILL: And the reason, because without the hectorites, and even with the hectorites, we are trying to read across from one compound -- one clay where we actually have data to clays that have a different quaternary compound or --

MS. BECKER: Okay.

DR. MARKS: Okay. Any other comments? If not, we'll move onto the next ingredient.

Day Two

DR. BERGFELD: … So, moving on to the next ingredient, Dr. Marks presenting the clays.

DR. MARKS: This the first time we've seen this draft report on the alkonium clays, their eight ingredients. We felt we could issue a tentative report with a safe conclusion. In the discussion we would talk about how we also use read across from the previous hectorite reports.

DR. BERGFELD: Is that a motion?

DR. MARKS: So, I move that we issue a tentative report with safe.

DR. BERGFELD: Dr. Belsito's Team, how do you stand?

DR. BELSITO: We were insufficient -- We are concerned about the stability of the enions in cosmetic formulation, particularly the benzalkonium and stearalkonium that could -- the ions seem -- the enions seem to be able to migrate out of the molecular --

DR. LIEBLER: The cations?

DR. BELSITO: The cations seem to be able to migrate under certain conditions, and we were curious whether those conditions would be present in a cosmetic formulation. Paul was concerned about inhalations, it seems to be used in powder, and the particle size of powder was potentially irrespirable, so we wanted information about the size of the molecules and the powder, and because of their use around the eye are, and our concern about release of potential irritants, we wanted ocular irritation at concentration of use, if available.

DR. BERGFELD: Dan, do you want to add to that at all, or?

DR. LIEBLER: Yeah. You know, I don't have a great deal of concern about the release of the --

DR. BERGFELD: Cations?

DR. LIEBLER: -- of the cation substituents, but we basically have no information, so I think we should try and get some additional clarification. I'd like to point out, although the hectorites provide some confidence in that respect, because we have pretty good safety assessments of those, I'm very reluctant to use the term read across, for inorganics are very complex molecules, because the concept we use as read across is more of a systematic evaluation of defined structures, of well-defined structures, and generally we apply it to organic molecules.

So, maybe we can use the term inference or, you know, hemileia, I just want to suggest that we avoid using the term read across when we are not strictly playing by the rules, the rules of read across.

Having said that, I think we should try and get some information about the release of some of the constituents, and Paul had comments on the powder.

DR. BERGFELD: Paul?

DR. SNYDER: So, we have chemical and physical properties that, say, at 30 percent of the ingredient is less than 10 microns, and so -- and it's used in both an aerosol and powder, and so our boilerplate covers the aerosol, but it doesn't cover the powder, and so I think we've got to be concerned about inhalation toxicity, because we know that 30 percent of the ingredient can be in irrespirable size range.

DR. BERGFELD: Thank you. Ron Hill?

DR. LIEBLER: If I may just clarify one thing that I just recalled from yesterday. I asked actually for two very specific things. Ones is the amount of the cation by weight, and the amount, if possible, to calculate the amount that's considered exchangeable under conditions that would be considered cosmetic ingredient.

So, the amount -- so we should give a specific request, we can get -- and the amount by weight would be useful, and then the amount exchangeable, if that can be provided, would also be useful.

DR. BERGFELD: Thank you. Ron Hill?

DR. HILL: I just wanted to say that I raised the inhalation issue yesterday and included in my needs particle size characterization further, in terms of actually in use, and I think I was shot down yesterday, but I had that concern.

DR. BERGFELD: Any other comments by the Marks' Team?

DR. MARKS: But I think I should retract my motion, and it sounds like this would be an insufficient data notice actually, not a tentative report.

DR. BELSITO: Right.

DR. MARKS: And I would second that insufficient data notice, certainly after -- with discussion.

DR. BERGFELD: And Don, can you repeat the needs that would be requested?

DR. BELSITO: Yes. So Dan wants to know the relative weight of the cations in the clay and their potential releasability in cosmetic formulation.

DR. LIEBLER: Yes. Because where we might end up -- sorry I keep feeling in the comments --

DR. BELSITO: It's the comment that's --

DR. LIEBLER: -- is that the amount of cations by weight is probably going to be much lower than the amount of clay by weight. And so, if we have those numbers then we can put a lower limit or an upper limit on the amount released and deal with it, because we will have safety data on the cations from other reports.

DR. BELSITO: Right. And then the molecular -- or the particle size for the powders, and then ocular irritation at highest concentration of use in the eye area, if available.

DR. BERGFELD: Thank you. Paul, did you have something to add? I saw your light on? No. All right. I think it's been -- Oh. Go ahead, Jim?

DR. MARKS: We did have the discussion by inhalation, and Lillian reminded me. Is Dr. Laba here? Who could make comments about what you said to our team yesterday? And we also discussed, certainly, clays are irritating, we know that, very irritating to put clay in the eye. We discussed that and I think it's obviously well to expand upon it, but we came to the conclusion in its use, and concentrations in eye shadow, mascara, that it was fine, but we'll get clarification.

DR. LABA: Yes. Dennis Laba with Presperse. I used to work with Elementis who manufactured these clays. They have been used in antiperspirant aerosols for years. The hectorite clay is much more than the bentonite clays, but they were used and they, as far as I know, still are being used.

The cation exchange capacity they -- in manufacture they watch that very carefully, because they don't want to add additional aqua more than they need, because it's expensive as well as, you know, really wouldn't be more efficacious. But the inhalation on the aerosols, I will try to get some further information from the manufacturers of the clays themselves. But if the FDA has anything on -- you know, antiperspirants because they are OTC drugs that would also help.

DR. BERGFELD: Thank you. Linda, I know this is not in your purview, but do you have a comment?

DR. KATZ: To be honest with you, I don't know if the data is available or not on the OTC side, and I guess the question that I would have if it's part of a monograph, the information may be old anyway. So that, you know, I really can't comment if the data is part of the FDA's background material or not.

If the question is, are we concerned about inhalation, in our discussions yesterday? I also mentioned that we had some concerns, and it will be useful if there is information for the Panel to

look at that information?

DR. BERGFELD: Thank you. Rachel, since I'm at that end of the table, how about any comments from you?

MS. WEINTRAUB: No. I would say that I think a common theme throughout this meeting is just how much information is needed to make informed decision of the Panel and through the -- at what point is the Panel comfortable with the information it has to move forward. And I think, certainly, from the consumer perspective, as much information as possible. You know, we think is the goal and to make informed decisions, so every support asking for information at all times, as existed.

And we think it's the responsibility of industry, you know, they are putting these ingredients in those instances, not all, but in most instances, in their products, so they should be able to share the data to justify its use.

DR. BERGFELD: Thank you, both. We are ready then, to move the question. This as I understand it, we'll go insufficient? Any other comments before we call the question? All those in favor please indicate by raising your hands; unanimous. Thank you. Moving on to a little bit more difficult group, and that's the citrus fruit group by Dr. Belsito.

(Motion passed unanimously)

Safety Assessment of Alkonium Clays as Used in Cosmetics

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ABSTRACT

This is a safety assessment of 8 alkonium clays, including stearalkonium bentonite, as used in cosmetics. These ingredients are reported to function as dispersing agents-nonsurfactant, emulsion stabilizers, and viscosity increasing agents-nonaqueous. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the relevant data related to these ingredients. Information on other alkonium clay-derived ingredients, including quaternium-18 bentonite and benzyl-dimethyl hydrogenated tallow ammonium montmorillonite clay, were used for inference purposes. The Panel concluded that these alkonium clays are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

INTRODUCTION

This is a review of the available scientific literature and unpublished data relevant to assessing the safety of alkonium clays as used in cosmetics. These ingredients are the products of the reactions of an ammonium salt with a smectite clay. The 8 alkonium clay ingredients in this report are:

- benzalkonium montmorillonite
- benzalkonium sepiolite
- hydrogenated tallowalkonium bentonite
- quaternium-18/benzalkonium bentonite
- quaternium-90 bentonite
- quaternium-90 montmorillonite
- quaternium-90 sepiolite
- stearalkonium bentonite

In cosmetics, these ingredients are reported to function as dispersing agents-nonsurfactant, emulsion stabilizers, and viscosity increasing agents-nonaqueous according to the *International Cosmetic Ingredient Dictionary and Handbook* (Table 1).[1]

Alkonium clays are derived from a group of phyllosilicate, layered, clay-based minerals (known as smectites), the most prominent of which are montmorillonite, beidellite, nontronite, saponite, bentonite, and hectorite. These alkonium clays are grouped together because of the similarities in physical structures and natures, chemical composition, exchangeable ion type, comparably small crystal size, and similarity of crystal natures of these minerals.

Other alkonium clay-derived ingredients, in particular quaternium-18 bentonite, have been reviewed by the CIR Panel and the information in these reports is useful for the determination of safety of the alkonium clays in this safety assessment. Summary data of quaternium-18 hectorite and the other previously reviewed ingredients are presented in Table 2. Ammonium hectorites (disteardimonium hectorite, dihydrogenated tallow benzylmonium hectorite, stearalkonium hectorite, and quaternium-18 hectorite), hectorite, quaternium-18 bentonite, hectorite, bentonite, montmorillonite and other clays and earths were found to be safe as used.[2-6]

Some of the components of the alkonium clays included in this safety assessment have been reviewed by the Panel and that data were useful in the determination of safety (Table 2). Quaternium-18 and stearalkonium chloride were determined to be safe as used, and benzalkonium chloride is safe up to 0.1% (upper limit of human irritation and sensitization assays).[7-9] Quaternium-90 has not been reviewed by the Panel. However, quaternium-90 and quaternium-18 are structurally similar (both are dialkyl dimonium chlorides, which vary only in fatty alkyl chain lengths, from palm oil and tallow, respectively); thus, information on quaternium-18 is relevant for inferring the safety of ingredients containing quaternium-90 and is included in this report.

Additionally, since quaternium-18 bentonite is useful for inference purposes in assessing the safety of the alkonium clays, data that have become available since the time of the quaternium-18 bentonite safety assessment are included in this safety assessment in the appropriate sections.

Descriptive data on the smectite clays (e.g., montmorillonite, bentonite, and sepiolite) that are useful in understanding the composition of the alkonium clays in this safety assessment are included.

Data on benzyl-dimethyl hydrogenated tallow ammonium montmorillonite clay were discovered on the European Chemicals Agency (ECHA) website.[10] While this is not the ingredient benzalkonium montmorillonite, the data for this clay is included because the similarity in chemical structures makes this information useful for inferring the safety of the ingredients in this safety assessment.

CHEMISTRY

Definition and Structure

Alkonium clays are the products of the reactions of an alkyl ammonium salt with smectite clay. Definitions of these ingredients are presented in Table 1.

Alkonium clays are derived from a group of phyllosilicate, layered, clay-based minerals, the general term for which is smectites, and the most prominent of which are montmorillonite, beidellite, nontronite, saponite, bentonite, and hectorite.[5] These clays are differentiated by variations in chemical composition involving substitutions of aluminum for silicon in tetrahedral cation sites and for aluminum, iron, magnesium, and lithium in octahedral cation sites (Figure 1).

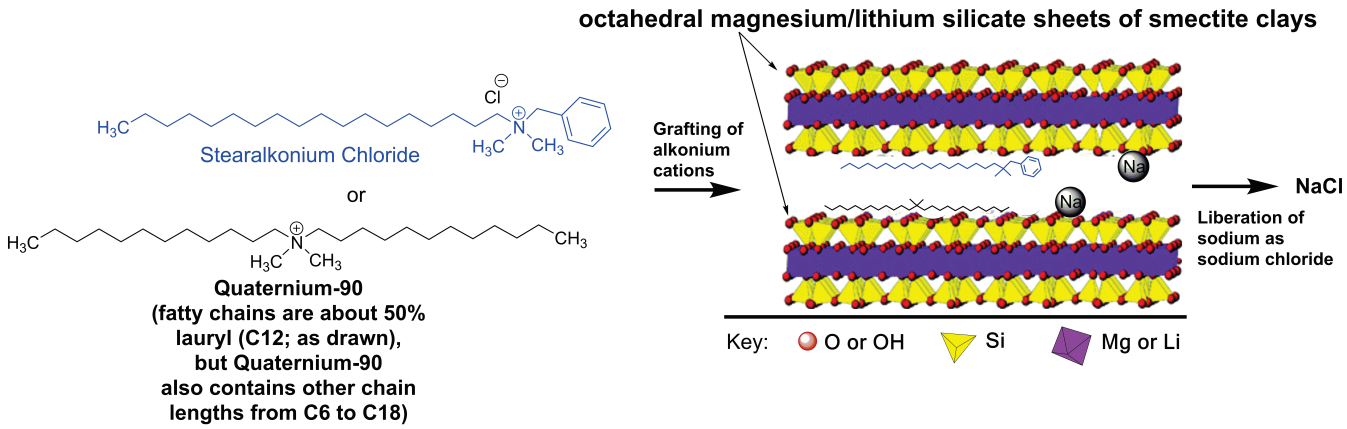

Figure 1. Synthesis of alkonium clays.

The smectite minerals are a subset of clays that include alkonium clays, and have a variable net negative charge that is balanced by sodium, calcium, or magnesium ions adsorbed externally on interlamellar surfaces.[5,11] The structure, chemical composition, exchangeable ion type, and small crystal size of smectite minerals are responsible for several unique properties, including a large chemically active surface area, a high cation exchange capacity, interlamellar surfaces having unusual hydration characteristics, and the ability to strongly modify the flow behavior of liquids. Because of isomorphous substitution of cations in the octahedral sheet during hectorite formation, the surfaces of these minerals have a delocalized net negative charge in the lattice. Cations located between 2 consecutive layers (octahedral sheets) compensate for the structural charge and keep the layers bound. Thus, cations such as sodium are attracted to the mineral surface to counterbalance the interlayer charge. These cations can be exchanged, because they are only retained in the mineral structure by electrostatic attractions.

The structures of alkonium clays depend on the charges of the layers and the lengths of the alkyl chains. Short-chain alkylammonium ions produce clays that are monolayered; clays containing long-chain alkylammonium ions are bilayered.[12,13] Smectites are highly charged and the alkyl moieties are composed of 3 kinked alkyl chains.[14] The basal spacing of alkylammonium smectites increases, in steps, with the alkyl-chain length.[15]

NATURAL SMECTITE CLAYS (BENTONITE, MONTMORILLONITE, AND SEPIOLITE)

Natural smectite clays (a.k.a. organoclays) are closely related, and the names have been used interchangeably to describe structurally similar clay minerals in the literature.[16] Natural deposits in which one of these clay minerals predominate are more commonly referred to by the predominant clay mineral's name. Thus, considering the similarity in the clay minerals of this category, the defining differentiation between the groups is the cation that is exchanged into the clay.

Bentonite is a widely distributed natural material consisting predominantly of the clay mineral montmorillonite, a smectite mineral.[11,16] Bentonite is formed of highly colloidal and plastic clays, and is produced by in-situ devitrification of volcanic ash.[17]

Montmorillonite occurs abundantly as dust at and near surface deposits of bentonite and is dispersed widely by air and moving water.[17] Montmorillonite is thus ubiquitous in low concentrations worldwide in soil, in the sediment load of natural waters, and in airborne dust. In geology, the term "montmorillonite" is ambiguous, and is used to refer to both a group of related clay minerals (where smectite is a more appropriate term) and to a specific member (montmorillonite) of that group.[18]

In structure, sepiolite can be considered transitional because it is structurally between the chain-structured and layer-structured silicates.[19,20] Sepiolite consists essentially of hydrated magnesium silicates with minor amounts of substituting elements.[21] Intracrystalline adsorption is limited in sepiolite due to the sizes of the channels in the crystal structure and the non-expanding nature of the clay. Therefore, only small and highly polar molecules interact with the "inner" surfaces, and nonpolar organic molecules absorb to external surfaces. Polar organic molecules can penetrate into the channels, but preliminary outgassing of the material is usually necessary to remove "zeolitic" water; for example, short-chain alcohols can penetrate into the channels after outgassing.

Sepiolite is found in sedimentary strata in arid and semi-arid climates around the world.[21] Deposits of sepiolite have been reported in China, France, Japan, Madagascar, Korea, Spain, Turkey, Tanzania, and the United States.[19,22,23]

Physical and Chemical Properties

With the exception of particle size information, chemical and physical properties were only discovered for stearalkonium bentonite (Table 3).

While the particle sizes represented below reflect the bulk size of these cation exchanged clay materials, if the cation were to be leachable it would of course be significantly smaller than these particles. However, data from one submission on these ingredients indicate that there is no appreciable leaching of this type.[24]

Stearalkonium bentonite particle sizes were reported to be: <100 µm, approximately 90%; < 10 µm, 30%; and < 0.5 µm, 0.02%.[25] The particle size ranges of hydrogenated tallowalkonium bentonite, benzalkonium montmorillonite, quaternium-90 montmorillonite, benzalkonium sepiolite, and quaternium-90 sepiolite are reported to be 90%-100% <100 µm, 20%-58% <10 µm, and none <0.1 µm.[26,27]

The sepiolite used to manufacture the ingredients in this safety assessment is reported to have a fiber length of 1-2 µm.[27]

The median particle size of quaternium-18 bentonite was reported to be 28 µm.[28]

In cosmetics, the ratios for cations used and clay for alkonium clays varies, depending on the type of cation and the type of clay.[28] The typical range for the cation is 20%-40% and the range for the clay is 60%-80%.

NATURAL SMECTITE CLAYS (BENTONITE, MONTMORILLONITE, AND SEPIOLITE)

Alkonium clays have a high capacity for expansion and swelling and can be easily hydrated and dehydrated.[29]

Intracrystalline adsorption is limited in sepiolite due to the sizes of the channels in the crystal structure and the non-expanding nature of the clays.[30] Therefore, only small and highly polar molecules interact with the "inner" surfaces, and nonpolar organic molecules absorb to external surfaces. Polar organic molecules can penetrate into the channels, but preliminary outgassing of the material is usually necessary to remove "zeolitic" water. For example, short-chain alcohols can penetrate into the channels after outgassing.

Bentonite has the ability to form thixotropic gels with water and absorb large quantities of water. It also has a high cation exchange capacity.[11] The absorption of water causes an accompanying increase in volume of as much as 12-15 times its dry bulk, which helps to confer the high cation exchange capacity. Freshly exposed bentonite is white to pale green or blue and darkens in time to yellow, red, or brown.[17]

Montmorillonite clay is composed of minute particles that, under electron microscopy, appear as aggregates of irregular or hexagonal flakes or, less commonly, thin laths.[31] Differences in substitution affect, and in some cases control, morphology.

Method of Manufacture

Alkonium clays are synthesized by grafting cationic surfactants to clay (i.e., exchanging the interlayer sodium cations with a cationic surfactant). These cationic surfactants are quaternary ammonium compounds with the template formula $[(CH_3)_3NR]^+$, $[(CH_3)_2NRR']^+$, and $[CH_3NRR'R'']^+$, where R, R', and R" are alkyl or arylalkyl hydrocarbons. For instance, in stearalkonium bentonite some of the inorganic cations of bentonite have been replaced by $[(CH_3)_2NRR']^+$, where R and R' are an octadecyl alkyl chain (i.e., stearyl group) and a benzyl group, respectively. The exchange is typically performed by the addition of the appropriate alkonium chloride (e.g., stearalkonium chloride) to an alcohol/water slurry of the clay.[32] The major by-products are inorganic chlorides (e.g., sodium chloride), which are removed during processing. This cation exchange shifts the nature of these minerals from hydrophilic to lipophilic.[32]

Impurities

As noted above, alkonium clays have a high cation exchange capacity.[11] Depending on the composition of a given cosmetic formulation, the degree to which these alkonium salts may be exchanged out of these ingredients will vary. Accordingly, there may be some resultant free alkonium salts.

Three alkonium bentonite clays with varying amounts of dimethyl dihydrogenated tallow quaternary ammonium chloride were dispersed in water at a level of 5% for 24 h.[24] When analyzed by high-performance liquid chromatography (HPLC), there was 10-20 ppm quaternary ammonium chloride present in the water phase (detection limit approximately 0.5 ppm); the saturation limit of dimethyl dihydrogenated tallow quaternary ammonium chloride is approximately 1500-2000 ppm.

Quaternium-90 bentonite was reported to have crystalline silica as an impurity at <3%.[28]

Stearalkonium bentonite may contain up to 5% quartz and up to 0.005% benzyl alcohol.[25] Benzalkonium sepiolite and quaternium-90 sepiolite were reported to be >95% pure with <0.5% silica/quartz.[27]

NATURAL SMECTITE CLAYS BACKGROUND (MONTMORILLONITE, BENTONITE, AND SEPIOLITE)

Clays contain trace elements, including antimony, arsenic, cadmium, cobalt, copper, lead, mercury, nickel, selenium, tellurium, thallium, and zinc in concentrations that are widely variable, depending on their geological origin.[33] These trace elements may be in the clay mineral structure or adsorbed on clay particles, which plays the most important role in controlling the distribution and abundance of these elements within these clays. Chemical elements in crystalline positions are usually locked in the clay, whereas those adsorbed may be mobilized and transferred to leaching solutions.

Natural bentonite may contain feldspar, cristobalite, and crystalline quartz.[34]

In an analysis of natural sepiolite samples from Japan, Spain, China, and Turkey, only the sample from China had small amounts of talc and calcite.[35]

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry in determining safety. The data received from the FDA are collected from manufacturers on the use of individual ingredients in cosmetics, by cosmetic product category, through the FDA Voluntary Cosmetic Registration Program (VCRP), and the data from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations, by category, conducted by the Personal Care Products Council (Council).

According to 2016 VCRP data, stearalkonium bentonite had the most reported uses at 388, including 385 leave-on uses and 3 rinse-off uses (Table 4).[36] The majority of these uses, 300, were in nail products, but this ingredient was also used in lipstick (63 uses) and in products used around the eye (7 uses). The only other ingredient with reported uses in the VCRP was quaternium-90 bentonite, which was reported to be used in 64 leave-on products, including 31 products used around the eye and 16 lipsticks.

In the 2015 survey conducted by the Council of the maximum use concentrations of ingredients in this group, stearalkonium bentonite was reported to be used at the highest maximum concentration at up to 6.5% in nail polish and enamel, 2.4% in lipstick, and 2.5% in eye shadow.[37-39] The ingredient with the next highest maximum concentration of use was quaternium-90 bentonite, which was reported to be used up to 6.1% in mascara and 6.1% in lipstick. It was confirmed by the Council that there were no reported uses of quaternium-90 bentonite in face powders; the face and neck product that was reported to be possibly a powder has been confirmed to be a lotion.

For 2 ingredients, no uses were reported to the VCRP, but use concentrations were provided in the industry survey. The VCRP did not report any uses for quaternium-90 montmorillonite, but the industry survey indicated that it is used in 2 types of leave-on formulations (foundations and aerosol suntan products) at concentrations up to 0.8%. No uses were reported by the VCRP for quaternium-90 sepiolite. However, the Council reported that it was used in 2 types of leave-on products (foundations and aerosol suntan products) at concentrations up to 3.2%. It should be presumed that both of these ingredients are used in at least 2 cosmetic formulations. It was reported that quaternium-90 montmorillonite and quaternium-90 sepiolite are sold together in a trade name mixture that is used in an aerosol suntan product.[40]

There were no reported uses in the VCRP or in the Council surveys for:

- hydrogenated tallowalkonium bentonite
- quaternium-18/benzalkonium bentonite
- benzalkonium montmorillonite
- benzalkonium sepiolite

Quaternium-90 montmorillonite is used in aerosol suntan products at concentrations up to 0.8% and quaternium-90 sepiolite is used in aerosol suntan products up to 3.2%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[41-44] 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.[41,44]

None of the alkonium clays named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[45]

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) of Australia concluded that stearalkonium bentonite did not pose an unreasonable risk to public health when used in cosmetic products at concentrations up to 5%; this was reported as the expected maximum concentration of use specified by the notifying companies.[25]

Non-Cosmetic

Large volumes of smectite clay minerals are used as a binder in foundry sand; a filter/clarifier/decolorizer; pet waste/odor absorbent; oil/grease absorbent; and pesticide carrier.[46] Smaller volumes are used in medical and pharmaceutical applications, building products, radioactive waste disposal, lubricants, detergents, seed coating, and water purification.

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Data on toxicokinetics of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Dermal – Non-Human

STEARALKONIUM BENTONITE

The dermal LD_{50} of stearalkonium bentonite was >2000 mg/kg (in deionized water) in Sprague-Dawley rats (n=5/sex).[25] The test was conducted in accordance with the Organization for Economic Cooperation and Development Test Guideline (OECD TG) 402.

Oral – Non-Human

STEARALKONIUM BENTONITE

The oral LD_{50} of stearalkonium bentonite was >5000 mg/kg (in corn oil) in albino Wistar rats (n=5/sex).[25] Clinical signs included matted fur and unkempt appearance on days 1 and 2 of observation. One male animal showed slight depression on day 4 prior to its death on day 5. At necropsy, a slightly reddened gastric mucosa was noted in a single rat. The test was conducted in a manner similar to the OECD TG 401.

BENZYL-DIMETHYL-HYDROGENATED TALLOW AMMONIUM MONTMORILLONITE CLAY

The reported oral LD_{50} for benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay was >5000 mg/kg in Sprague-Dawley rats (n not specified).[10]

Inhalation – Non-Human

Data on the acute inhalation toxicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided. However, data on similar ingredients were found and are included.

QUATERNIUM-18 BENTONITE

In an acute inhalation study of quaternium-18 bentonite (average concentration 5.7 mg/L; particle size ≥10 µm, 30% ≤10 µm) in Sprague-Dawley rats (n=5/sex), the rats were exposed for 4 h 22 min in a glass chamber and were observed post exposure for 14 days.[47] There were no mortalities and no irreversible signs of toxicity observed.

BENZYL-DIMETHYL-HYDROGENATED TALLOW AMMONIUM MONTMORILLONITE CLAY

The reported inhalation LC_{50} for benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay was >206 mg/L when Sprague-Dawley rats (n not specified) were exposed for 1 h.[10] Particle size was not specified.

Repeated Dose Toxicity

Dermal

Data on the repeated dose dermal toxicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

Oral – Non-Human

STEARALKONIUM BENTONITE

In a 28-day oral toxicity test of stearalkonium bentonite (100, 316, and 1000 mg/kg in 0.1% aqueous solution of Na-carboxymethylcellulose) in Fischer CDF(F344)/CRLBR, SPF rats (n=5/sex), the no-observed-effect-level (NOEL) was 1000 mg/kg/d when administered by gavage, based on the absence of test substance-related toxicological effects at any of the doses administered.[25] The test was conducted according to OECD TG 407. Clinical signs were similar in the treatment and control groups. Chromodakryorrhoea was observed occasionally in both the control and treatment groups. There were no differences in feed consumption or body weight gain in males. Decreased body weights were recorded for females in the high dose recovery group (duration of recovery period not specified), but were considered by the study authors to be of no toxicological relevance. No differences were observed in hematology or clinical biochemistry parameters, appearance of spontaneous lesions, or organ weight changes in the males, and no dose-related trends observed at necropsy or by histopathology examination. Decreases in organ weights in the females (heart and brain) at the end of recovery period were considered to be of no toxicological relevance, because there were no corresponding differences observed at the end of the exposure period.

Inhalation

Data on the repeated dose inhalation toxicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on reproductive and developmental toxicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

GENOTOXICITY

In Vitro

STEARALKONIUM BENTONITE

Stearalkonium bentonite (3.16, 10, 31.6, 100, and 316 µg/plate, with and without metabolic activation, in dimethyl sulfoxide) was not genotoxic to *Salmonella typhimurium* (strains TA98, TA100, TA102, TA1535, and TA1537).[25] The positive control yielded the expected results. Pronounced cytotoxicity was noted in all test strains at 316 µg/plate, with and without metabolic activation. In the assays without metabolic activation, cytotoxicity was also noted in several strains at 31.6 and/or 100 µg/plate. The test was performed in accordance with OECD TG 471.

QUATERNIUM-18 BENTONITE

An Ames assay was conducted on quaternium-18 bentonite (10, 30, 100, 300, 3000 µg/plate) in *S. typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) with and without metabolic activation.[48] There were no signs of genotoxicity at any concentration with and without metabolic activation.

In Vivo

STEARALKONIUM BENTONITE

In a micronucleus assay, conducted in accordance with OECD TG 474, stearalkonium bentonite (1000, 1500, and 2000 mg/kg in 0.1% aqueous solution of Na-carboxymethylcellulose) was not clastogenic in Crl:NMRI BR mice (n=5/sex) when administered by gavage.[25] There were no mortalities prior to scheduled killing. The ratios between the polychromatic and normochromatic erythrocytes in the female mice at all doses were similar to that of the control data. However, the ratios were greater in males at all doses at 24 h. Because the values were within the historical negative control data ranges, the differences were not considered to be attributable to the test substance. The number of micronucleated polychromatic erythrocytes in the high dose groups (both sexes) was higher than that of the corresponding negative control group 48 h after administration. However, all counts were within the range of historical negative control data, thus the study authors considered the effect to be unrelated to the treatment. The concurrent negative and positive controls produced the expected results.

CARCINOGENICITY

Data on carcinogenicity of the alkonium clays in this safety assessment were not found in the published literature and no unpublished data were provided.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

STEARALKONIUM BENTONITE

Stearalkonium bentonite (100%) was not irritating to the intact or abraded skin of New Zealand White rabbits (n=6) when administered under occlusion for 24 h.[25] The test was conducted in accordance with OECD TG 404 and the test sites were examined at 24 and 72 h after patch removal. The mean erythema/eschar and edema scores for the intact sites were 0 out of 4; the mean erythema/eschar score for the abraded sites was 0.3, and the edema score was 0.25.

The maximum non-irritating concentration for stearalkonium bentonite injected intradermally was 1.25% in distilled water when tested in albino Hartley guinea pigs (n not specified).[25] The maximum non-irritating concentration when administered topically to the skin was 60% in distilled water. No further details were provided.

Dermal - Human

QUATERNIUM-90 BENTONITE

In a 48-h patch test (n=21) of a mascara containing quaternium-90 bentonite (5.924%), it was concluded that the mascara was appropriate for consumer use.[49] No further information was provided.

Ocular-In Vivo – Non-Human

STEARALKONIUM BENTONITE

Stearalkonium bentonite (100%; 0.1 g) was severely irritating when instilled into the conjunctival sac of New Zealand White rabbits (n=7).[25] The test was conducted in accordance with OECD TG 405 and the rabbits were observed for 7 days after exposure. If the test substance was still present in the eye at 24 h after exposure, the eye was rinsed with distilled water. The most severe outcome observed for conjunctiva/redness was grade 3 (diffuse beefy red) in all rabbits 24 h after instilling the test substance. By day 7, only 1 rabbit exhibited a grade 2 response (more diffuse, crimson red, individual vessels not easily discernible). A grade 4 response for conjunctiva/chemosis (swelling with lids about half-closed to completely closed) was observed in 5 of 6 rabbits examined 24 h post exposure. One rabbit in this group exhibited a grade 2 response (obvious swelling with partial eversion of the lids) on day 7. The highest score for conjunctiva/discharge of grade 3 (discharge with moistening of the lids and hairs and of a considerable area around eye) was observed in 2 of 6 rabbits at 24 h

post exposure. This was resolved by day 7. Corneal opacity of grade 2 (easily discernible translucent areas, details of iris slightly obscured) was observed in 2 of 6 rabbits at 24 h post exposure. A highest score of grade 3 (opalescent areas, no details of iris visible, size of pupil barely discernible) was observed in 1 of 6 animals at 48 h post exposure. One rabbit still exhibited a grade 4 for opaqueness; the iris was invisible on day 7. Five of 6 rabbits exhibited a grade 1 iridial inflammation response (sluggish reaction) with the effect persisting in 1 rabbit through day 7.

Stearalkonium bentonite (31-36 mg in 0.1 mL; vehicle not specified) was slightly irritating to the conjunctiva of female New Zealand White rabbits (n =3).[25] Neither cornea nor irises were affected. Slight conjunctival redness was observed in 2 rabbits from 1 through 48 h after exposure. Slight-to-moderate chemosis of the conjunctiva was observed in 2 rabbits at 1 through 48 h after exposure. Ocular discharge was noted in 2 rabbits from 1 to 24 h after administration. The test was conducted in accordance with OECD TG 405.

Ocular-In Vivo – Human

QUATERNIUM-90 BENTONITE

A 4-week use study (n=53; group 1: 21 with sensitive eyes, group 2: 11 with non-sensitive eyes, group 3: 21 wore contact lenses) of an eyeliner that contained quaternium-90 bentonite (2.75%) was conducted.[50] Biomicroscopic and peri-ocular examinations were performed on both eyes and the eyes were examined for functional signs prior to and after the first use and after the last use. Also, on the right eye of groups 1 and 2, a colormetric examination was performed on the cornea and conjunctiva, and a tear film break-up time measurement was performed. The contacts lenses of group 3 were examined before and after the test period. The eyeliner was applied once or twice per day on the upper and lower eyelids of both eyes; no other eye makeup was to be used during the test. Ocular irritation of slight to moderate intensity was reported in 2 subjects (1 with sensitive eyes and 1 with contact lenses). Ocular discomfort of slight intensity and short duration was reported in 1 subject wearing contact lenses. Palpebral irritation of slight to moderate intensity and long duration was reported in 1 subject with sensitive eyes and 1 wearing contact lenses. One subject with sensitive eyes was reported to have a conjunctival redness of slight intensity and long duration at the final examination of the eyes. The authors concluded that this product presented good ocular comfort, good ocular safety, and was well tolerated in subjects with sensitive eyes and contact lenses.

In a 1-week use study (n=25) of a mascara containing quaternium-90 bentonite (5.699%), there were no adverse reactions reported.[51]

Ocular-In Vitro

QUATERNIUM-90 BENTONITE

An eyeliner that contained quaternium-90 bentonite (2.75%) was predicted to be a weak irritant in a bovine cornea opacity/permeability (BCOP) assay.[52]

In 6 separate hen's egg tests-utilizing the chorioallantonic membrane (HET-CAM), 6 mascara products containing quaternium-90 bentonite (4.0275%) were predicted to be practically non-irritating.[53-58]

In an EpiOcular assay, a mascara containing quaternium-90 bentonite (5.924%) had an ET_{50} (estimated time to reduce cell viability by 50%) of 13.5 h.[59] It was concluded that this was "acceptable".

Sensitization

Dermal – Non-Human

STEARALKONIUM BENTONITE

Stearalkonium bentonite was not sensitizing to albino Hartley guinea pigs (n=20) when topically administered at 60% (in distilled water) during the induction phase and topically at 30% and 60% during the challenge phase.[25] There were no signs of sensitization at 24 and 48 h after the challenges. The test was conducted in accordance with OECD TG 406. The test sites were treated with 10% lauryl sodium sulfate in petroleum jelly prior to the induction phase.

QUATERNIUM-18 BENTONITE

A Draize test of quaternium-18 bentonite (0.1% in a physiological solution containing 2% Tween 80) was conducted using guinea pigs (n=12).[47] The test substance was administered intracutaneously at 0.05 mL on the first dose and at 0.01 mL for the remaining doses. The injections were administered 3 times per week for a total of 10 doses. Two weeks after the final induction, the challenge dose (0.05 mL) was administered. There was no evidence of hypersensitivity observed in any of the guinea pigs. Quaternium-18 bentonite was not a sensitizer under these test conditions.

Dermal - Human

There were no signs of irritation or sensitization in human repeated insult patch tests (HRIPT) of several products containing various alkonium clays at up to 4.3% (Table 5).[60-64]

SUMMARY

This is a review of the available scientific literature and unpublished data assessing the safety of alkonium clays as used in cosmetics. Alkonium clays are derived from a group of phyllosilicate, layered, clay-based minerals, including

montmorillonite, saponite, bentonite, and hectorite. These ingredients are grouped together because of the similar chemical structures, chemical composition, exchangeable ion type, and small crystal size of these minerals.

In cosmetics, these ingredients are reported to function as dispersing agents-nonsurfactant; emulsion stabilizers; viscosity increasing agents-nonaqueous.

Other alkonium clay-derived ingredients have been reviewed by CIR; ammonium hectorites (disteardimonium hectorite, dihydrogenated tallow benzylmonium hectorite, stearalkonium hectorite, and quaternium-18 hectorite), hectorite, quaternium-18 bentonite, hectorite, bentonite, montmorillonite and other clays and earths were found to be safe as used

Data on quaternium-18 bentonite were relied on for inference purposes; this includes new data (included in this Summary) and data from the previous report.

When alkonium bentonite clays with varying amounts of dimethyl dihydrogenated tallow quaternary ammonium chloride were dispersed in water at a level of 5% for 24 h, there was 10-20 ppm quaternary ammonium chloride present in the water phase; the saturation limit of dimethyl dihydrogenated tallow quaternary ammonium chloride is approximately 1500-2000 ppm.

Stearalkonium bentonite had the most reported uses at 388 including 385 leave-on uses and 3 rinse-off uses; it was reported to be used up to 6.5% in nail polish and enamel, 2.4% in lipstick, and 2.5% in eye shadow. Quaternium-90 bentonite was reported to be used in 64 leave-on products; it was reported to be used up to 6.1% in mascara and up to 6.1% in lipstick. It was confirmed by the Council that there were no reported uses of quaternium-90 bentonite in face powders and that a face and neck product reported to contain quaternium-90 bentonite was a lotion, not a powder.

The dermal LD_{50} of stearalkonium bentonite was >2000 mg/kg in rats.

The oral LD_{50} of stearalkonium bentonite was >5000 mg/kg in rats. The oral LD_{50} for benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay was >5000 mg/kg in rats.

The reported inhalation LC_{50} for benzyl-dimethyl-hydrogenated tallow ammonium montmorillonite clay was >206 mg/L in rats when exposed for 1 h. There were no mortalities and no irreversible signs of toxicity observed in rats in an acute inhalation study of quaternium-18 bentonite at an average concentration of 5.7 mg/L with an exposure of over 4 h.

In a 28-day oral toxicity test of stearalkonium bentonite, the NOEL was 1000 mg/kg/d in rats.

Stearalkonium bentonite was not genotoxic to *S. typhimurium* (strains TA1535, TA1537, TA98, TA100, and TA102). It was cytotoxic at 316 µg/plate, without and with metabolic activation. In the tests without metabolic activation, cytotoxicity was also noted in several strains at concentrations of 31.6 and/or 100 µg/plate. In a micronucleus assay, stearalkonium bentonite was not clastogenic in mice when tested at doses up to 2000 mg/kg. In an Ames assay conducted on quaternium-18 bentonite in *S. typhimurium*, there were no signs of genotoxicity up to 1000 µg/plate with and without metabolic activation.

Stearalkonium bentonite was not irritating to intact or abraded skin of rabbits at 100%. The maximum non-irritating concentration for stearalkonium bentonite was 1.25% when injected intradermally and was not irritating when topically applied to the skin at a concentration of 60% in guinea pigs.

In a human patch test of a mascara containing quaternium-90 bentonite at 5.924%, it was concluded that the mascara was appropriate for consumer use.

In one study, stearalkonium bentonite was a severe ocular irritant when instilled into the eyes of rabbits at 100%. In another study, stearalkonium bentonite at 31-36 mg/ 0.1 mL was slightly irritating to rabbit eyes. Neither cornea nor irises were affected.

An eyeliner containing quaternium-90 bentonite at 2.75% was well tolerated in a 4-week use test. In a 1-week use study of a mascara containing quaternium-90 bentonite at 5.699%, there were no adverse reactions reported.

An eyeliner that contained quaternium-90 bentonite at 2.75% was predicted to be a weak ocular irritant in a BCOP assay. In 6 HET-CAM assays, 6 mascara products containing quaternium-90 bentonite at 4.0275% were predicted to be practically non-irritating. In an EpiOcular assay, a mascara containing quaternium-90 bentonite at 5.924% had an ET_{50} of 13.5 h.

Stearalkonium bentonite was not sensitizing to guinea pigs when topically induced with a 60% solution and challenged topically with 30% and 60% solutions. There was no evidence of hypersensitivity observed in guinea pigs in a Draize Test of quaternium-18 bentonite at 0.1%.

There were no signs of irritation or sensitization in HRIPTs of several cosmetic products containing various alkonium clays at up to 4.3%.

DISCUSSION

The CIR Expert Panel examined the available data on alkonium clays, which consists mostly of data on stearalkonium bentonite and quaternium-90 bentonite. The data included acute oral, dermal, and inhalation toxicity, oral repeated dose toxicity, genotoxicity, and dermal irritation and sensitization data. The data also include use studies and in vitro assays of products used near the eyes. The Panel also considered the data available from safety assessments of previously reviewed alkonium clay ingredients, in particular quaterium-18 bentonite; new data on quaternium-18 bentonite were also evaluated. Because there were multiple genotoxicity assays with negative results from this and the previous hectorite and ammonium hectorite safety assessments, the Panel was comfortable that these ingredients are not carcinogenic.

Some of the components of these alkonium clays may be formed from plant-derived or animal-derived constituents and the clays used as cosmetic ingredients are derived from clays extracted from the ground. The Panel expressed concern

regarding pesticide residues and heavy metals that may be present in the botanical-derived ingredients (e.g., quaternium-90-derived ingredients) as well as heavy metals that may be present in the clays. They stressed that the cosmetics industry should continue to use good manufacturing practices to sufficiently limit amounts of such impurities in ingredient before blending them into cosmetic formulations. Additionally, the Panel considered the dangers inherent in using animal-derived ingredients (e.g. quaternium-18/benzalkonium bentonite and hydrogenated tallowalkonium bentonite), namely the transmission of infectious agents. While tallow may be used in the manufacture of ingredients in this safety assessment and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the U.S. FDA that tallow derivatives are not risk materials for transmission of infectious agents.

These ingredients are generally large molecules, and dermal penetration should be negligible. However, it was noted that the manufacture of these ingredients includes cation exchanges conducted under mild conditions (e.g., low temperatures and neutral pH), suggesting that the cations could be released from these ingredients in cosmetic formulations. However, the quaternary ammonium compounds were shown to be stable within these alkonium clays under mild conditions and solubility in water was very low, therefore, this concern is not warranted. Also, possible dissociates, stearalkonium chloride and quaternium-18, were found to be safe as used in previous safety assessments and benzalkonium chloride is safe up to 0.1 %.

Tests for potential ocular irritation at the maximum concentration of use (6.1%) were not available for these ingredients, but there were use studies of a mascara and an eyeliner containing quaternium-90 bentonite up to 5.699% with negative results. These studies were sufficient to determine that ocular irritation is unlikely at maximum use concentrations.

The Panel discussed the issue of incidental inhalation exposure from aerosol suntan products because these ingredients are reportedly used at concentrations up to 3.2% in cosmetic products that may be aerosolized. There were no inhalation studies of these ingredients, but there were acute inhalation data on quaternium-18 bentonite and on dihydrogenated tallow benzylmonium hectorite, quaternium-18 hectorite, calcium silicate, and benzalkonium chloride in previous safety assessments. The Panel noted that 95%-99% of particles would not be respirable to any appreciable amount. Furthermore, particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the properties of these ingredients. 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 effects. 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 alkonium clay ingredients listed below are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating:

- benzalkonium montmorillonite*
- benzalkonium sepiolite*
- hydrogenated tallowalkonium bentonite*
- quaternium-18/benzalkonium bentonite*
- quaternium-90 bentonite
- quaternium-90 montmorillonite
- quaternium-90 sepiolite
- stearalkonium bentonite

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

TABLES

Table 1. Definitions and functions of the alkonium clays in this safety assessment.[1]

Ingredient CAS No.	Definition	Function
Hydrogenated Tallowalkonium Bentonite	Hydrogenated Tallowalkonium Bentonite is the product of the reaction of hydrogenated tallowalkonium chloride and bentonite.	Viscosity increasing agent-aqueous
Quaternium-18/ Benzalkonium Bentonite	Quaternium-18/Benzalkonium Bentonite is a reaction product of bentonite and quaternium-18 and benzalkonium chloride.	Dispersing agent-nonsurfactant
Quaternium-90 Bentonite 226226-22-8	Quaternium-90 Bentonite is a reaction product of bentonite and quaternium-90.	Dispersing agent-nonsurfactant
Stearalkonium Bentonite 130501-87-0	Stearalkonium Bentonite is a reaction product of bentonite and stearalkonium chloride.	Dispersing agent-nonsurfactant
Benzalkonium Montmorillonite	Benzalkonium Montmorillonite is the reaction product of benzalkonium chloride and montmorillonite.	Dispersing agent-nonsurfactant; emulsion stabilizer; viscosity increasing agent-nonaqueous
Benzalkonium Sepiolite	Benzalkonium Sepiolite is the product obtained by the reaction of benzalkonium chloride and sepiolite.	Dispersing agent-nonsurfactant; emulsion stabilizer; viscosity increasing agent-nonaqueous
Quaternium-90 Montmorillonite	Quaternium-90 Montmorillonite is the product obtained by the reaction of quaternium-90 and montmorillonite.	Dispersing agent-nonsurfactant; emulsion stabilizer; viscosity increasing agent-nonaqueous
Quaternium-90 Sepiolite	Quaternium-90 Sepiolite is the product obtained by the reaction of quaternium-90 and sepiolite.	Dispersing agent-nonsurfactant; emulsion stabilizer; viscosity increasing agent-nonaqueous

Table 2. Data on related ingredients to the alkonium clays in this safety assessment.

Related ingredient	Summary data	Reference
Ammonium Hectorites - Quatemium-18 Hectorite, Disteardimonium Hectorite, Dihydrogenated Tallow Benzylmonium Hectorite, and Stearalkonium Hectorite	Safe as used; highest concentration of use: disteardimonium hectorite in makeup preparations at 28%. Single dose (acute) toxicity-oral :LD_{50} dihydrogenated tallow benzylmonium hectorite, 5.0 g/kg for rats; quaternium-18, >10 g/kg. Single dose (acute) toxicity-inhalation: LC_{50} dihydrogenated tallow benzylmonium hectorite, >5.2 mg/L for rats after 4 hours; aerosolized quaternium-18 hectorite was not toxic to rats at 202 mg/L after 1 h. Repeated dose toxicity: Stearalkonium hectorite was not dermally toxic to rabbits at concentrations of 12.5% to 50% over 3 weeks. Quaternium-18 hectorite administered to the skin of rabbits for 3 weeks was not toxic up to 50%. Genotoxicity: Stearalkonium hectorite was not mutagenic to *S. typhimurium* up to 1500 µL/plate or mouse lymphoma cells up to 500 µL/plate. Dermal irritation and sensitization: Stearalkonium hectorite did not cause erythema or edema to albino rabbits at 50% w/v. Quaternium-18 hectorite at 50% was not irritating to rabbits. Dihydrogenated tallow benzylmonium hectorite at 0.5 g in 0.5 mL saline was not irritating when administered to the intact and abraded skin of rabbits. Disteardimonium hectorite was not irritating to humans in 2 patch tests at 15%. Stearalkonium hectorite was not irritating or sensitizing to humans at 100%. Dihydrogenated tallow benzylmonium hectorite (concentration not provided) did not cause delayed contact hypersensitivity in albino guinea pigs. Quaternium-18 hectorite was not irritating or sensitizing up to 100% in HRIPTs. Ocular irritation: Stearalkonium hectorite was a minimal to mild ocular irritant to rabbits and humans. It was classified as a minimal to mild irritant in 3 Eyetex in vitro tests of products. Quaternium-18 hectorite was not an ocular irritant at 50% in rabbits and at 2 mg in humans. Dihydrogenated tallow benzylmonium hectorite at 0.5 g in 0.5 mL saline was practically nonirritating when administered to the eyes of rabbits.	[5]
Quaternium-18 Bentonite, Quaternium-18, and Quaternium-18 Hectorite	Safe as used; highest concentration of use: Review-quaternium-18 hectorite in eyeshadow, blushers, other makeup preparations, and suntan products, 10%; quaternium-18 in hair conditioners, 10%; quaternium-18 bentonite in lipstick, 10%. Re-review-quaternium-18 hectorite in other personal cleanliness products, 19%; quaternium-18 bentonite in mascara, 9%; quaternium-18 in hair tonics and dressings, 2%. Absorption, distribution, metabolism, and excretion: Quaternium-18 hectorite and bentonite are chemically, physically, and biologically inert. Quaternium compounds are poorly absorbed through the skin. Single dose (acute) toxicity-oral and percutaneous: Acute oral and percutaneous toxicity tests in animals indicate that all three compounds exhibit little or no systemic toxic effects. The oral LD_{50} of quaternium-18 bentonite was 8 g/kg in rats. Single dose (acute) toxicity-inhalation: Quaternium-18 hectorite was nontoxic in an acute	[2,4,5]

Table 2. Data on related ingredients to the alkonium clays in this safety assessment.

Related ingredient	Summary data	Reference
	inhalation study. Repeated dose toxicity- oral and dermal: Subchronic oral and dermal toxicity tests on quaternium-18 and quaternium-18 bentonite presented no evidence of systemic toxicity. There were no signs of toxicity in rats fed diets containing up to 25% quaternium-18 bentonite for 12 weeks. There was no evidence of local or systemic toxicity of quaternium-18 bentonite observed when administered to the depilated skin of rabbits under occlusion for 6 h/day for 90 days. Irritation and sensitization: All 3 quaternium compounds were considered to cause at most only slight irritation to animal skin. None has been reported to be skin sensitizing agents in animals. In clinical studies, quaternium-18 is practically nonirritating and nonsensitizing to the skin. Quaternium-18 hectorite and quaternium-18 bentonite can be classified as a nonirritating, "nonfatiguing," and nonsensitizing agent. Undiluted quaternium-18 bentonite at 0.5 g applied to both intact and abraded rabbit skin for 6 h/day for 5 consecutive days, and again after 10 days of rest for 5 more days elicited no reaction and was considered to be inert. Quaternium-18 bentonite at 0.1% was not sensitizing to guinea pigs. In an HRIPT of two eyebrow color preparation containing quaternium-18 bentonite at 4.1%, there was no evidence of skin irritation, "fatiguing," or sensitization observed. Ocular irritation: In ocular irritation studies in rabbits, all 3 ingredients have been shown to be at most mild irritants. Quaternium-18 Bentonite at 10% was not an ocular irritant in rabbits. Quaternium-18 hectorite exhibits no ocular irritation in humans. Phototoxicity: Quaternium-18 Hectorite does not present any adverse phototoxic or photoallergenic effects.	
Hectorite, Bentonite, Montmorillonite, Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Pyrophyllite, and Zeolite	Safe as used; highest concentration of use: Hectorite in skin cleansing preparations; Kaolin in other skin care preparations at 100%. Absorption, distribution, metabolism, and excretion: No absorption of aluminum and elevated levels of silicon were recorded in assayed plasma samples of dogs given magnesium trisilicate and zeolite orally; the urinary excretion of silica was 5.2% in males given 20 g of magnesium trisilicate. Single-dose (acute) toxicity-oral: oral LD_{50} of hectorite, >5 g/kg in rats; calcium silicate, 3400 mg/kg in rats; magnesium aluminum silicate, >50000 mg/kg in mice; zirconium silicate, > 200 g/kg in mice; kaolin, 149 g/kg in rats (death due to bowel obstruction); 15 natural zeolites, 10 g/kg in rats. Single-dose (acute) toxicity-dermal: The acute dermal LD_{50} was >3.5 g/kg for rabbits exposed to 4% magnesium aluminum silicate. Repeated dose toxicity-oral: In short-term oral toxicity studies, no adverse effects were seen in mice or rabbits dosed up to 5 g/kg magnesium aluminum silicate; beagle dogs and rats fed aluminum silicate had no renal lesions. Dogs and rats fed magnesium trisilicate for 4 weeks had polydypsia and polyuria, and all dogs had renal cortical lesions. Guinea pigs had renal lesions after 4 months of drinking magnesium trisilicate in their tap water. Rats fed 10% magnesium aluminum silicate had slightly elevated silicon levels of the spleen and dogs and rats fed 10% magnesium aluminum silicate had no negative responses in 90-day feeding studies. No lesions were found in rats dosed up to 1000 mg/kg for 104 weeks. Various zeolites added to the diets of pigs caused no adverse effects. Repeated dose toxicity-inhalation: Small primary neoplastic lesions were found in 2 rats exposed to a calcium silicate sample in an inhalation chamber. The mass of silicate measured in the lungs ranged from 0.1-0.8 mg. Lebrija and Leichester Attapulgite samples caused 1 peritoneal mesothelioma, one adenocarcinoma, and 3 bronchoalveolar hyperplasia and 2 mesotheliomas, 1 peritoneal mesothelioma, 1 malignant alveolar tumor and eight bronchoalveolar hyperplasia (inhalation route) in rats, respectively. Both samples contained long fibers. Moderate to extensive respiratory disease was noted in rats chronically exposed to synthetic zeolite A by inhalation methods. Irritation and sensitization: Hectorite was nonirritating to the skin of rabbits in a Draize primary skin irritation study. Magnesium aluminum silicate (4%) was a weak primary skin irritant in rabbits and had no cumulative skin irritation in guinea pigs. No gross effects were reported in any of these studies. Sodium magnesium silicate (4%) had no primary skin irritation in rabbits and had no cumulative skin irritation in guinea pigs. Ocular irritation: Bentonite caused severe iritis after injection into the anterior chamber of the eyes of rabbits. When injected intralamellarly, widespread corneal infiltrates and retrocorneal membranes were recorded. In a primary eye irritation study in rabbits, hectorite was moderately irritating without washing and practically nonirritating to the eye with a washout. A 4% solution of magnesium aluminum silicate and a 4% solution of sodium magnesium silicate caused minimal eye irritation in a Draize eye irritation test. Rats tolerated a single dose of zeolite A without any adverse reaction in the eye. Reproductive and developmental toxicity: Calcium silicate (250 to 1600 mg/kg) had no effect on nidation or on maternal or fetal survival in rabbits. Magnesium aluminum silicate (6000 mg/kg) had neither a teratogenic nor adverse effects on the mouse fetus. Female rats receiving a 20% kaolin diet exhibited maternal anemia but no reduction in birth weight of the pups was recorded. Type A zeolite produced no adverse effects on the dam, embryo, or fetus in either rats or rabbits at any dose level (74 or 1600 mg/kg). Clinoptilolite had no effect on female rat reproductive performance. Genotoxicity: In the *S. typhimurium* LT2 spot test (TA98, TA100, TA1535, TA1537, and	6

Table 2. Data on related ingredients to the alkonium clays in this safety assessment.

Related ingredient	Summary data	Reference
	TA1538) with or without metabolic activation, magnesium aluminum silicate and hectorite were found nonmutagenic. No increase mutation frequencies were seen in the *Salmonella* TA1530 or G-46 assay and no increase in recombinant activity in the *Saccharomyces* D3 assay treated with calcium silicate was observed. A subacute dose of 150 mg/kg of calcium silicate produced 3% breaks in bone marrow cells arrested in c-metaphase. In a metaphase spread of bone marrow cells, calcium silicate produced no increase in the number of aberrations compared to controls and in a dominant lethal assay did not induce any dominant lethal mutations. In primary hepatocyte cultures, the addition of attapulgite had no significant unscheduled DNA synthesis (UDS) response or modulated response to AAF (a positive control); attapulgite at 10 $\mu g/cm^2$ caused increases in UDS in rat pleural mesothelial cells. Zeolite particles (<10 µm*)* produced an increase in the percentage of aberrant metaphases, mostly chromatid breaks. Irritation and sensitization: Applications of 2 g of magnesium aluminum silicate to the skin of 2 humans daily for 1 week caused no effects. Occupational studies: In occupational exposure studies of mineral dusts, fibrosis and pneumoconiosis has been documented in workers involved in the mining and processing of aluminum silicate, calcium silicate, zirconium silicate, fuller's earth, kaolin, montmorillonite, pyrophyllite, and zeolite.	
Benzalkonium Chloride	Safe up to 0.1%; highest concentration of use: 0.1%; 0.5% in a liquid towelette Single dose (acute) toxicity-oral: Acute oral LD_{50} for rats dosed with benzalkonium chloride ranged from 342 to 525 mg/kg. Single dose (acute) toxicity-dermal: Of 96 mice receiving dermal applications of 6.5 and 50% benzalkonium chloride, 29 died within 72 h after application. Repeated dose toxicity-oral: In a subchronic toxicity study, benzalkonium chloride solutions were administered via stomach tube to 40 albino rats for 12 weeks (once/day) at dosages of 50.0 mg/kg (1:20 dilution) and 100.0 mg/kg (1:10 dilution). Two of 20 rats receiving the 100.0 mg/kg dosage died. In a chronic toxicity study, benzalkonium chloride (10.0%) was administered via stomach tube to 18 beagle dogs at dosages of 12.5, 25.0, and 50.0 mg/kg for 52 weeks (once daily). One of 6 dogs receiving 50 mg/kg dosages and 3 of 6 dogs receiving 25 mg/kg dosages died. Repeated dose toxicity-inhalation: No adverse effects were noted when rats and hamsters inhaled a conditioner containing 0.1% benzalkonium chloride over a period of 13 consecutive weeks (4 h/day). Irritation and sensitization-nonhuman: Benzalkonium chloride concentrations of 1.0%-50% induced reactions ranging from erythema to necrosis when applied to the skins of rabbits. In another study, 24-h applications of 1.0% to 10.0% benzalkonium chloride to the skins of rabbits resulted in severe induration. Benzalkonium chloride concentrations of 1.0% and 5.0% induced epidermal necrosis when applied (24-h exposure) to the skins of albino guinea pigs. Applications of 2.0% benzalkonium chloride to the skins (abraded and intact) of rabbits resulted in severe erythema (2-day application period). Slight erythema was noted 7 days after application. Applications of 1.0% benzalkonium chloride to the skins of white rats during a 2-month period caused hyperemia and necrosis. Following applications of 0.5% benzalkonium chloride to the skins of rabbits (24 h exposure), severe erythema, moderate edema, and eschar formation were observed. Benzalkonium chloride (0.5%) resulted in practically no skin irritation when applied to the skins of albino rabbits (24-h exposure). When 0.1% benzalkonium chloride was applied to the skins of rabbits (5-day contact period), slight erythema and necrosis were observed. These reactions were observed for 3 weeks post-treatment. Irritation and sensitization-human: Cutaneous reactions were observed in 2 of 399 dermatitis patients patch tested with benzalkonium chloride over a period of 64 months. In separate studies, primary irritant dermatitis was observed in 13 patients and 12 patients patch tested with 10.0% benzalkonium chloride (24-h exposure). In another study, erythema was observed in 33 of 70 leprosy patients patch tested with 2.5% benzalkonium chloride. Benzalkonium chloride concentrations of 0.5%, 1.0%, and 2.0% induced several pustular and/or bullous reactions in 26 of 55 patients (48-h exposures). The application of 17.0% benzalkonium chloride (24-hour period) to the skin of each of 21 subjects resulted in well-defined erythema (13 subjects). Confluent erythema and edema were noted in the skin of subjects tested with 5.0% and 2.5% benzalkonium chloride (12-h exposure). Results from a 21-day skin irritation study of a cream containing 0.1% benzalkonium chloride indicated essentially no cumulative irritation. A cream containing 0.1% benzalkonium chloride did not induce skin irritation or sensitization reactions in 101 subjects patch tested during a 6-week period (24-h exposures). Sensitization reactions were observed in 6 of 100 patients patch-tested with 0.07% benzalkonium chloride. The 6 patients also had positive reactions to 0.05%, 0.025%, and 0.01% benzalkonium chloride. Sixty-six of 2,806 patients were sensitive to 0.1% benzalkonium chloride. In another study, allergic reactions were observed in 9 of 142 patients patch tested with 0.1% benzalkonium chloride. Sensitization reactions were not observed in normal subjects patch-tested with 0.1% benzalkonium chloride. Ocular irritation: Benzalkonium chloride at 1% and 2.0% aqueous induced severe iritis and severe conjunctival injection, respectively, when instilled into the conjunctival sac of rabbits twice daily for 7 days. Benzalkonium chloride (0.3%) induced minimal ocular irritation when instilled once into the eyes of rabbits. Single instillations of 0.1% benzalkonium chloride into the conjunctival sac of albino rabbits did not cause ocular	[7,8]

Table 2. Data on related ingredients to the alkonium clays in this safety assessment.

Related ingredient	Summary data	Reference
	irritation. The instillation of 0.1% benzalkonium chloride into the conjunctival sacs of rabbits 5 times daily for 1 week resulted in corneal damage. The instillation of 0.01% benzalkonium chloride into the conjunctival sacs of rabbits (5 min-6-h period) resulted in cornea1 damage. Four hours after the instillation of 0.5%, 1.0%, and 10% benzalkonium chloride, cornea1 damage was noted in rabbits and guinea pigs. The ocular administration of 0.5%, 1.0%, and 2.0% solutions twice daily for 7 days caused conjunctival damage in rabbits. Following the daily administration of 0.007% and 0.1% benzalkonium chloride for 2 weeks, retinal detachment was observed in pigmented but not albino rabbits. In in vitro intraocular toxicity studies, the exposure of rabbit corneas to benzalkonium chloride concentrations ranging from 0.0001% to 0.01% resulted in cornea1 damage. Exposure periods ranged from 2 min (0.01%) to 110 min (0.0001%). The longest exposure was 180 min (0.0065%). Slight conjunctival hyperemia was observed in 1 of 51 human subjects who received ocular instillations of 0.02% benzalkonium chloride. Reproductive and developmental toxicity: The instillation of 100 or 208 mg/kg of aqueous benzalkonium chloride into the vaginas of pregnant rats resulted in sternal defects in the offspring. Genotoxicity: Benzalkonium chloride was not mutagenic to *S. typhimurium* (strains TA1535, TA1536, TA1537, and TA1538) and *E. coli* (strains B/r WP2 her^+ and WP2 her^-) in microbial test systems making up the ret-assay in combination with reverse mutation systems. Mutagenic activity also was not demonstrated in reversion assays involving *S. typhimurium* (strains TA1535, TA1536, TA1537, and TA1538) and, in the ret-assay, with *Bacillus subtilis* (strains H17 Ret^+ and M45 Rec^-). In the plate incorporation assay, benzalkonium chloride was not mutagenic to *S. typhimurium* (strains TA98, TA1538, TA1537, and TA100). In the *E. coli* DNA polymerase assay benzalkonium chloride induced repairable DNA damage in strains W3110 (pol A+) and p3478 (pol A-). Carcinogenicity: The dermal application of 8.5% and 17% benzalkonium chloride to rabbits and mice did not result in tumor formation or systemic toxic effects, but did produce ulceration and inflammation at the application sites.	
Stearalkonium Chloride	Safe as used; highest concentration of use: review, 5%, re-review, 7%. Single dose (acute) toxicity-oral: The oral LD_{50} of stearalkonium chloride in rats ranged from 0.5-1.25 g/kg. Repeated dose toxicity-oral: In mice, an LD_{50} value of 0.760-0.113 g/kg was reported in a 7-day oral study. Irritation and sensitization: In single application dermal studies with concentrations of up to 25%, stearalkonium chloride produced minor irritation in rabbits. A repeated insult patch test with a 1% aqueous solution of stearalkonium chloride on 50 human subjects showed the material to be neither a primary irritant nor a sensitizer. A single 48-hour patch test with challenge 2 weeks later indicated that 20% stearalkonium chloride was not a sensitizer. Ocular irritation: In acute eye studies in rabbits, a 25% solution of stearalkonium chloride was a severe irritant. Concentrations of 1.25% and less were slightly and transiently irritating to the rabbit eye.	[4,9]

Table 3. Chemical and physical properties of stearalkonium bentonite.

Property	Value	Reference
Stearalkonium bentonite		
Density/Specific Gravity @ 25 °C	330-480	[25]
Melting Point °C	>390	[25]
Boiling Point °C	>500	[25]
Water Solubility g/L @ 20 °C	$<0.04 \times 10^{-3}$	[25]
log K_{ow} @ 25°C	5.87 (estimated)	[25]

Table 4. Frequency of use according to duration and exposure of alkonium clays.[36-39]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Quaternium-90 bentonite		Quaternium-90 montmorillonite		Quaternium-90 sepiolite		Stearalkonium bentonite	
Total/range	**64**	**0.41-6.1**	**NR**	**0.4-0.8**	**NR**	**1.6-3.2**	**388**	**0.051-6.5**
Duration of use								
Leave-on	64	0.41-6.1	NR	0.4-0.8	NR	1.6-3.2	385	0.19-6.5
Rinse-off	NR	0.63	NR	NR	NR	NR	3	0.051
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type[a]								
Eye area	31	0.41-6.1	NR	NR	NR	NR	7	0.19-2.5
Incidental ingestion	16	6.1	NR	NR	NR	NR	63	0.5-2.4
Incidental Inhalation-sprays	2[b]	NR	NR	0.8[d]	NR	3.2[d]	1[c]	NR
Incidental inhalation-powders	2[b]	NR	NR	NR	NR	NR	NR	NR
Dermal contact	35	0.41-4	NR	0.4-0.8	NR	1.6-3.2	25	0.19-2.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	0.46-0.5	NR	NR	NR	NR	300	0.015-6.5
Mucous Membrane	16	6.1	NR	NR	NR	NR	65	2.4
Baby	NR	NR	NR	NR	NR	NR	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

[a] 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.

[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[d] In this case, quaternium-90 montmorillonite and quaternium-90 sepiolite are sold as a trade name mixture. This mixture is used in an aerosol suntan product.

Table 5. HRIPTs of cosmetic products containing alkonium clays.

Ingredient(s); product; concentration	n; details	Results	Reference
Quaternium-90 Bentonite; mascara; 4.3%	102; Modified Draize test with 9 administrations (3x/week). Patches on the scapula were removed after 24 h. After a 2-week rest, the test substance was administered to a naïve site and observed at 24, 48, and 72 h after removal.	There were no reactions to indicate irritation or sensitization during the induction or challenge phases.	60,61
Quaternium-90 Bentonite; foundation; 2.2%	102; 9 administrations (3x/week). Patches (1"x1") were allowed to volatize for several minutes prior to placement on the scapula and were removed after 24 h. After a 2-week rest, the test substance was administered to a naïve site and observed at 24, 48, and 72 h after removal. After a 2-week rest, the test substance was administered to a naïve site and observed at 24 and 72 h after removal.	There was no indication of irritation or allergic contact sensitization.	63
Stearalkonium Bentonite ; lipstick; 1.452%	100; test substance was applied to a patch pad and remained in the open air for 15-20 min before administration to the infrascapular area of the back or the upper arm for 24 h. There were 9 administrations in the induction phase.	There were no signs of irritation or sensitization.	64
Quaternium-90 Sepiolite and Quaternium-90 Montmorillonite in a spray leave-on product; 3.2% and 0.8%, respectively[a]	56; The test substance (0.2 mL) was administered to the upper back on 0.75" x 0.75" occlusive patches and left for 24 or 48 h for 9 administrations.	There were no signs of irritation or sensitization.	62

[a] Quaternium-90 montmorillonite and quaternium-90 sepiolite (at 0.8% and 3.2%, respectively) in this case are a trade name mixture.

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2016 VCRP Data for Alkonium Clays

03B - Eyeliner	STEARALKONIUM BENTONITE	6
03C - Eye Shadow	STEARALKONIUM BENTONITE	1
03G - Other Eye Makeup Preparations	STEARALKONIUM BENTONITE	1
07C - Foundations	STEARALKONIUM BENTONITE	3
07E - Lipstick	STEARALKONIUM BENTONITE	68
07I - Other Makeup Preparations	STEARALKONIUM BENTONITE	6
08A - Basecoats and Undercoats	STEARALKONIUM BENTONITE	16
08C - Nail Creams and Lotions	STEARALKONIUM BENTONITE	4
08E - Nail Polish and Enamel	STEARALKONIUM BENTONITE	348
08F - Nail Polish and Enamel Removers	STEARALKONIUM BENTONITE	1
08G - Other Manicuring Preparations	STEARALKONIUM BENTONITE	17
10E - Other Personal Cleanliness Products	STEARALKONIUM BENTONITE	4
12F - Moisturizing	STEARALKONIUM BENTONITE	1
		476

03A - Eyebrow Pencil	QUATERNIUM-90 BENTONITE	2
03B - Eyeliner	QUATERNIUM-90 BENTONITE	2
03C - Eye Shadow	QUATERNIUM-90 BENTONITE	10
03D - Eye Lotion	QUATERNIUM-90 BENTONITE	1
03F - Mascara	QUATERNIUM-90 BENTONITE	13
03G - Other Eye Makeup Preparations	QUATERNIUM-90 BENTONITE	4
07C - Foundations	QUATERNIUM-90 BENTONITE	8
07E - Lipstick	QUATERNIUM-90 BENTONITE	16
07I - Other Makeup Preparations	QUATERNIUM-90 BENTONITE	4
12C - Face and Neck (exc shave)	QUATERNIUM-90 BENTONITE	2
12J - Other Skin Care Preps	QUATERNIUM-90 BENTONITE	3
		65

No reported uses in the 2016 VCRP data for:

Hydrogenated Tallowalkonium Bentonite
Quaternium-18/Benzalkonium Bentonite
Quaternium-90 Montmorillonite
Quaternium-90 Sepiolite
Benzalkonium Montmorillonite
Benzalkonium Sepiolite

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 15, 2016

SUBJECT: Comments on the Revised Tentative: Safety Assessment of Alkonium Clays as Used in Cosmetics (tentative report posted on the CIR website January 6, 2016)

Key Issue

Physical and Chemical Properties - Please provide a reference for the following sentence: "While the particle sizes represented below reflect the bulk size of these cation exchanged clay materials, if the cation were to be leachable it would of course be significantly smaller than these particles." This sentence is not consistent with the information provided by Elementis. They indicated that in general these ingredients are 60% to 80% clay, and that in water little of the quaternary ammonium cations dissociated. Without a reference, this sentence should be deleted as it is not known what would happen to particle size in a cosmetic formulation that contains other ingredients that could also interact with clay.

Additional Considerations

Introduction - The Introduction states that information on benzyl-dimethyl hydrogenated tallow ammonium montmorillonite "may be useful for inferring the safety of the ingredients in this safety assessment." This should be revised to be consistent with the Abstract that says that the information was "used for inference purposes."

Method of Manufacture - In the first sentence, please delete "Clay minerals, such as" - as the clay minerals themselves are not manufactured by the stated methods.

Cosmetic Use - The original summary of concentration of use information from the Council did not indicate the form of the face and neck product (other than saying it was not a spray). Therefore, the statement "the face and neck product that had been reported to be a powder was a lotion" needs to be revised to: "the face and neck product that may have been a powder was a lotion."

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Summary - Please also mention the reviews of Stearalkonium Chloride, Quaternium-18 and Benzalkonium Chloride in the Summary.

Table 2, Quaternium-18 Bentonite - Please revise the following sentence: "There was no evidence of local or systemic toxicity of quaternium-18 bentonite was observed when administered to the depilated skin of rabbits under occlusion for 6 h/day for 90 days."

Hectorite, Bentonite, Montmorillonite, et al. - In what species was the urinary excretion of silica "5.2% in males given 20 g of magnesium trisilicate"? Please revise the following sentence: "No increase mutation frequencies were seen in the *Salmonella* TA-1530 or G-36 assay and no increase in recombinant activity in the *Saccharomyces* D3 assay treated with calcium silicate."

Benzalkonium Chloride and Stearalkonium Chloride - The use information for both of these ingredients is from the CIR re-reviews, but the only citations provided are to the original reports. The CIR re-reviews of these ingredients need to be added as references to this report.

Table 4 - What is the source of the 0.051% concentration for Stearalkonium Chloride? The Council use survey included a concentration of 0.015% in nail polish and enamel removers; perhaps the digits of this value have been transposed?