BLUE

Safety Assessment of Alumina and Aluminum Hydroxide as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	August 16, 2013
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The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, 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 and Ivan Boyer, Ph.D. D.A.B.T., Senior Toxicologist.

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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
Ivan Boyer, PhD. D.A.B.T.
Senior Toxicologist

Date: August 16, 2013

Subject: Draft Final Safety Assessment For Alumina and Aluminum Hydroxide As Used In Cosmetics

In June, the Panel reviewed the draft report of alumina and aluminum hydroxide and issued a conclusion of safe as used in cosmetics. Attached, please find the Draft Final Report for your consideration. There were no public comments and no new data were submitted. The comments from industry were addressed.

The Panel had requested a section on neurotoxicity to be added to address the public's perception of a connection between aluminum and Alzheimer's disease. However, after considering the other issues that were also connected to aluminum, the staff created a section on aluminum toxicity. This discusses the current state of research for osteomalacia, dialysis encephalopathy, breast cancer, as well as Alzheimer's disease. This will provide information on all of the possibilities of aluminum toxicity for the Panel's consideration.

The Panel should review the Draft Final Report and ensure that the Abstract, Discussion, and Conclusion reflect the Panel's thinking. The Panel should issue a Final Report.

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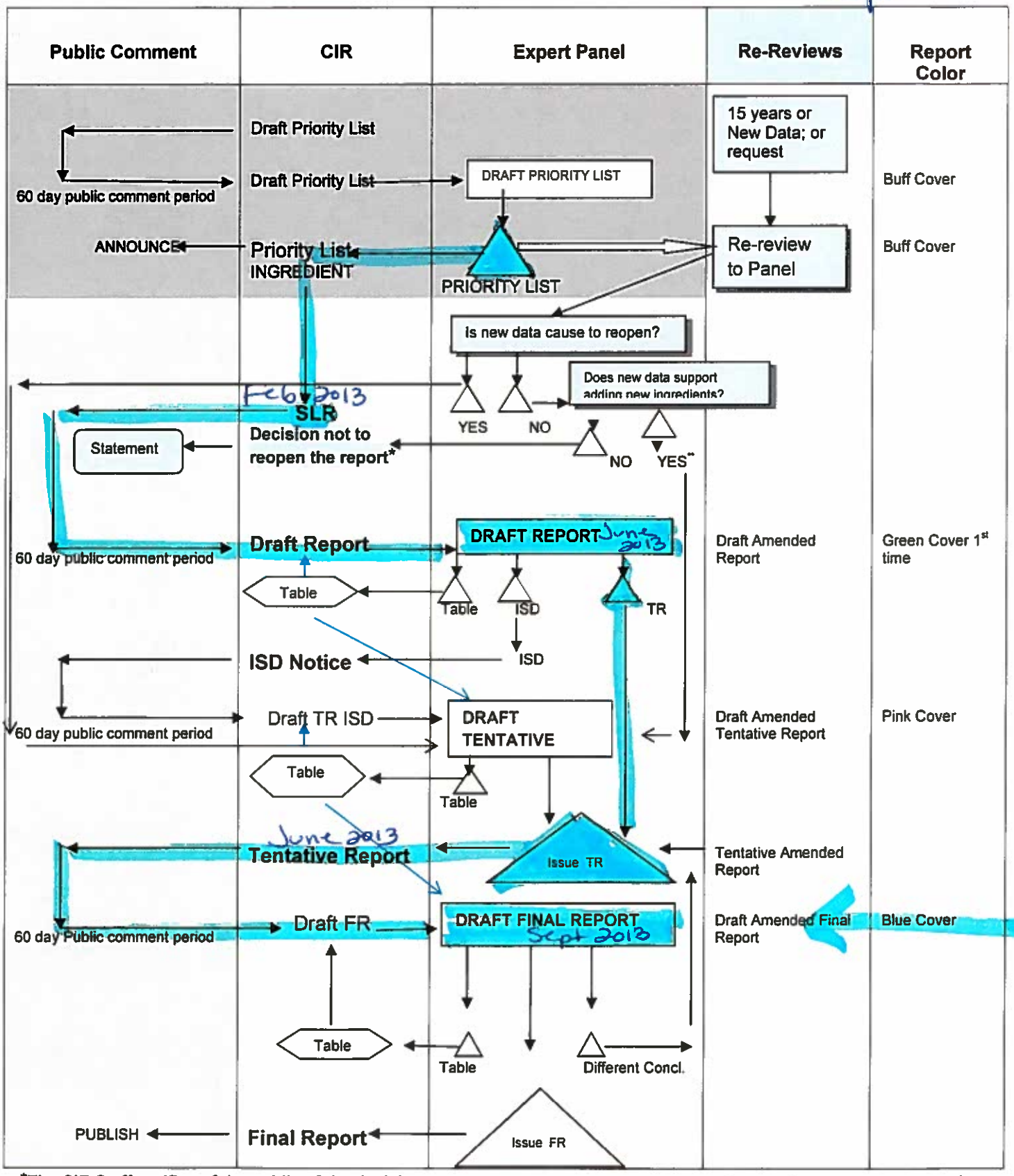
Alumni

SAFETY ASSESSMENT FLOW CHART

Sept 2013



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

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

△ Expert Panel Decision

History of Alumina and Aluminum Hydroxide

February, 2013 - SLR is posted for public comment.

June, 2013 – Panel examined the draft report. The Panel was satisfied with the use of FDA's evaluation of these ingredients in medical devices and OTC medications for use in evaluation of their safety in cosmetics. There was discussion on the public's perception of aluminum and how that connects to these ingredients.

September, 2013 – The Panel examines the Draft Final Report and ensures that the Abstract, Discussion, and Conclusion reflect the Panel's thinking. The Panel should review the new section on aluminum toxicity to ensure that it covers the issues that the Panel considers necessary.

Alumina and Aluminum Hydroxide Data Profile for September, 2013. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitiza-tion					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Alumina																		
Aluminum Hydroxide							X				X				X			

Since CIR is depending on FDA's assessments of these ingredients, only data that augments the information has been included in this report.

Search Strategy for
Alumina and Aluminum Hydroxide

Names and CAS Nos. in **SciFinder –** Discovered multiple patents for medical devices using alumina. Also discovered multiple patents and references to aluminum hydroxide and antacids.

Searched **FDA website** for alumina and for the types of medical devices found in SciFinder. Also searched for aluminum hydroxide in pharmacuticals.

Mined report on aluminum for data on aluminum hydroxide.

Minutes for ALUMINA & ALUMINUM HYDROXIDE
From June, 2013

DR. MARKS' TEAM

DR. MARKS: Okay. Shall we move on? Next is alumina and aluminum hydroxide. And this is the first time we've seen these ingredients.

And, Ron and Tom, do you have any needs?

DR. SHANK: No, thanks.

DR. MARKS: And I guess the question, we aren't going to eliminate. They're two simple compounds, right, that say -- one is compound, one is an element, I guess.

MS. BECKER: No.

DR. MARKS: No.

MS. BECKER: Not aluminum. It's alumina.

DR. SHANK: Do we need skin sensitization here?

DR. MARKS: Yeah, that's what I had. There's no -- so the aluminum hydroxide, it's a non-irritant at 10 percent. We have aluminum hydroxide being used at 60 percent, and there's no sensitization data at all. So I'd like to see an HRIPT. I was thinking of having an insufficient data notice.

DR. SHANK: Because the product is marked, "If continued use produces irritation, stop using it."

MR. ANSELL: For the hydroxide?

DR. MARKS: Yes.

DR. SHANK: Well, it contains --

MR. ANSELL: I mean, most of it says don't eat them. There's an envelope in the bottom of your packet.

DR. SHANK: I don't have the product, but I saw -- I checked it on the web, and there was some not warnings, but informational note, shall we say, if repeated use produces irritation, stop using it.

DR. MARKS: So that wasn't in this report.

DR. SHANK: No.

DR. MARKS: I'm glad I didn't miss that. I was wondering where was it.

DR. SHANK: But there's no --

MS. BECKER: Where do you see that?

DR. MARKS: No, that was --

DR. SHANK: On the website for --

MR. ANSELL: Probably the OTC applications.

DR. SHANK: I can't remember now.

MS. BECKER: Okay.

DR. SHANK: I don't put a whole lot of credibility in those things, but on the other hand --

MS. BECKER: Is that alumina or the aluminum hydroxide?

DR. SHANK: It was an antiperspirant.

DR. MARKS: So it's more than likely aluminum oxide.

MR. ANSELL: I don't know that --

DR. SHANK: But that's the difference between a deodorant and antiperspirant, isn't it, aluminum?

MR. ANSELL: Well, no. I mean, it's a regulatory distinction. One is cosmetic and that makes you smell better, and one actually causes you to stop perspiring.

DR. HILL: But if you have an antiperspirant, it will have aluminum trichloride or aluminum zirconium, something, heptachloride, heptide. So, yes.

MR. ANSELL: But they're aluminum salts, not oxides or hydroxides.

DR. HILL: Yes.

MS. BECKER: Yes, but aluminum – but antiperspirants are not in our purview. Only deodorants are.

DR. HILL: Yes, I know.

MR. ANSELL: But it is a good point because we were curious as to the -- I'm sorry. Go ahead.

DR. SHANK: Well, there's a lot of reference to antiperspirants in the report.

MS. BECKER: Right.

DR. SHANK: Did I read the wrong thing? Antiperspirants, and we even go into the mechanism of action, plugging the --

MS. BECKER: Right.

DR. SHANK: -- sweat gland ducts and things.

MS. BECKER: Yes, for the information that it provides for sensitization, irritation, et cetera.

DR. SHANK: Right.

MS. BECKER: But as for the actual antiperspirants, they're not in ours. They're not considered a cosmetic.

DR. HILL: I assume that data was there primarily to look about absorbability, right, because most of that plugged into places where we would ask the question is it absorbable, because those kinds of effects depend on having soluble compounds like aluminum trichloride or like the aluminum zirconium complex.

And alumina is complete insoluble. Aluminum hydroxide is practically insoluble. So those kinds of things practically don't pertain.

DR. MARKS: So because it's insoluble, you wouldn't think you need sensitization, because that's what I had on mine as the aluminum.

DR. SLAGA: I didn't think you needed it because --

DR. MARKS: I did see that, and that's fine. I just -- where does it say here? It's GRAS. Somewhere it says it's the third hardest. What was that? Third hardest ingredient.

MS. BECKER: Third hardest.

DR. SHANK: It's in the report.

MS. BECKER: Substance.

DR. SHANK: After diamond and carbonundrum. But if it's totally insoluble, how do you make a buffer from it? It's totally insoluble at --

DR. MARKS: Where does it say buffer? I see bulking, pacifying agent. Oh, yeah, there we go, "function as a buffering agent, corrosive and a pH adjuster."

MR. ANSELL: The hydroxide is.

DR. SLAGA: Yeah, the hydroxide.

DR. MARKS: Yeah.

MR. ANSELL: Oxide.

DR. SHANK: Yeah. The first sentence on page 9 in PDF under "physical and chemical properties," the very first paragraph, the second sentence, "alumina and aluminum hydroxide are white insoluble solids." Now, if an aluminum hydroxide is insoluble, how do you use it as a buffer?

DR. HILL: So it functions as a solid proton sponge is the way you look at that.

DR. SHANK: The solid?

DR. HILL: Yeah.

DR. SHANK: Proton sponge.

DR. HILL: Seriously. I'm not making that up. It functions as a solid proton sponge.

MR. ANSELL: It's not a hydroxide. It's a --

DR. SHANK: That may make sense to you. Does it make sense -- I don't know what that is, a chemical sponge.

DR. HILL: Okay. So you take alumina -- excuse me -- aluminum hydroxide, and it's a solid.

DR. SHANK: Yes.

DR. HILL: And you put it in the presence of, say, diluted hydrochloric acid.

DR. SHANK: Acid, okay.

DR. HILL: All right. And so – it isn't completely insoluble. It's very insoluble.

DR. SHANK: But not in dilute hydrochloric acid.

DR. HILL: Right, because then you're taking --

DR. SHANK: So, like, in stomach gastric juices?

MR. ANSELL: Like Tums.

DR. MARKS: Yeah, so we aren't -- to me it's not concerning on the skin then as far as sensitization. If it's insoluble, then we don't need the sensitization data.

DR. SHANK: Right.

DR. MARKS: Okay, so --

DR. SLAGA: "Safe as used."

DR. MARKS: Okay, "safe."

DR. SHANK: Well --

DR. MARKS: Well, that's why I say are there any needs. So the hydroxide is not an irritant at 10 percent, which I think is reassuring because it could be an irritant. And that's the concentration that's used. So we don't need -- so I think the insufficient data notice, and said "safe," but, Ron, you had a hesitation. Let's not go so fast. What were you going to say, Ron?

DR. SHANK: Well --

DR. MARKS: Hold on. Let me get this working.

DR. SHANK: The chemicals added to cosmetic preparations have aluminum in non-soluble form, non-ionized form, and then, yeah, "safe as used."

DR. MARKS: I'm sorry. I was trying to multitask and not very successfully. What did you say? What did you want to do?

DR. SHANK: As long as we know that the aluminum compounds added to cosmetics, alumina and aluminum hydroxide are not soluble in the cosmetic product.

DR. MARKS: That's a whole different situation.

DR. SHANK: Well, you read this and it sounds like, you know, this stuff is just not soluble. And then there are all kinds of gels and pH adjusters and things like that, which I mean, yes, they are, or they can be.

MR. ANSELL: What would be the concern about the aluminum ion?

DR. SHANK: None for me, but then you should have to discuss breast cancer and Alzheimer's because the literature is full of that concern in the public. I don't think the evidence is convincing at all. We came across this once before in a review. Somebody used an aluminum something deodorant. They did an epidemiological study in women who used this deodorant, had more breast cancer than women who did not. I don't remember what that was.

MR. ANSELL: It was the doctor's studies, but it was a paraben preservative. But there is aluminum cookware which was associated --

DR. SHANK: With Alzheimer's.

MR. ANSELL: Well, yeah, shows it on the Internet as causing Alzheimer's.

DR. SHANK: Okay, but there was one about a deodorant. Was it a paraben?

SPEAKER: I think it was -- I know there's one other, aluminum and paraben, they're --

DR. SHANK: Breast cancer unless, you know, the oxter is so close to the GRAS than -- and we have that in our discussion.

DR. HILL: Well, I think the -- yes. And antiperspirants, again, is present as either the trichloride or the aluminum zirconium complex. I presume that those are not used in deodorants because if they were used in deodorants, it would be an antiperspirant, and anyway, we're not reviewing those. We're reviewing aluminum hydroxide and alumina.

MS. BECKER: Right.

DR. HILL: What adds to the confusion based on what's in here is that you if you take an aluminum hydroxide tablet, there will be some absorption of aluminum, if you take Tums or Maalox or Mylanta. It's because in the milieu of the gut and, in particular, the stomach where we drop down the pH-2 on fasted stomach, you will actually convert some of that aluminum hydroxide, a small amount, to something else. And even then if you look, the absorption is very small. But then the pharmacy students learn if you've got somebody's who's renally compromised, it's a potential problem because over time the chloride can build up. That's totally irrelevant to any of these ingredients in a cosmetic exposure.

But the point is that it's no longer aluminum hydroxide that allows it be absorbed. It's because in the milieu of the gut where it's being able to react with the hydrochloric acid in the stomach, you get some soluble aluminum species. And in humans, that absorption is, like, .2 percent, I think is what it's in here. So, none of that is really relevant. I think if you had a mouthwash and somebody was drinking it, I guess that's potentially an issue, but, I mean, that's so far- fetched for me as to be --

MR. ANSELL: The topical would be – the absorption of aluminum for topical applications, even the hydroxide, you know, it's poorly absorbed.

DR. HILL: Because the hydroxide is so insoluble.

DR. SHANK: Well, it's in lipstick, right?

MR. ANSELL: Well then, we have special oral --

DR. SHANK: So then you do get ingestion and it goes into the gastric juice.

DR. HILL: But the amounts --

DR. SHANK: It's all very, very small, but what's --

DR. HILL: Very small. Very small indeed.

DR. SHANK: 8.8 percent concentration in lipstick. So I think we need to discuss this in the discussion, okay?

MR. ANSELL: I think that's absolutely appropriate.

DR. MARKS: Okay. Any other?

MS. BECKER: So which points did you -- exactly how do you want to attack that?

DR. HILL: Carefully.

DR. SHANK: That the Panel recognizes that there is potential for ingestion, and insolubilization. Put it that way. But the amounts would not be of toxicological concern. And then I'm not too sure how I feel about this. Is it necessary to mention the literature that makes an association between aluminum? They don't say what form aluminum in breast cancer and aluminum in Alzheimer's.

MS. BECKER: Oh, to give some of the stuff from next door, a lot of that is addressed by making sure that in the introduction that we are talking alumina and not aluminum, and they're different.

DR. SHANK: Yeah, but if it gets dissolved in the gastric juice, then you're not talking about alumina.

MS. BECKER: Right.

DR. SHANK: You're talking about aluminum ions.

DR. MARKS: So if you state, Ron --

DR. SHANK: Okay. I don't think it's a problem at all.

DR. MARKS: Right.

DR. SHANK: On the other hand, our reviews are closely monitored by several groups of consumers and people who are interested in what goes into cosmetics.

MS. BECKER: Yes.

DR. SHANK: And since the literature is -- the popular literature, okay. If you Google "Alzheimer's" and "aluminum," you're going to get a lot, a lot of hits. If you "breast cancer" and "aluminum," you're going to get a lot, a lot hits. The information -- the public awareness is there, and I think we need to ask ourselves do we need to add this to the discussion or not.

DR. MARKS: So you're really saying should it be specific or just in a general, not enough of toxicologic concern, and leave it at that, and not be saying specifically the controversy over breast and --

DR. SHANK: Oh, no, the Panel thinks it's really light, as long as there's no toxicological concerns.

DR. MARKS: Yeah. I like that.

DR. SHANK: And leave it at that.

DR. MARKS: That's kind of how I would do it, but it's up to -- you know, Tom, Ron, do you like it at that rather than open the Pandora's box with -- so are we -- and then the reason we aren't -- despite your issue of, well, what if it's in a preparation that's non-aqueous, then how much is insoluble, and we move forward as far as the sensitization. We're not concerned because it's not soluble?

DR. HILL: It would be even less soluble, either of those ingredients, in an non-aqueous --

DR. MARKS: Okay.

DR. HILL: -- formulation of any kind. I was surprised that people didn't ask the question either, inhalation toxicity because there are inhaled exposures, and ocular irritation, because those are the only things that came up with me. And probably it's because I've used aluminum chromatography a bit, and very similar concerns with silica in terms of -- but, you know, I know what we found in silica. So I don't know -- I don't have any real concerns, but I just wondered if anybody else thought about that because there are inhaled inhalation exposure, most incidental. And it's in the products used in neighborhood of the eye. We do have, depending on the form of the alumina, potential for exposure to very fine particulates. I'll for now toss that out there.

DR. MARKS: It didn't raise a concern for me.

DR. HILL: It didn't me either. I think I prefaced it by saying, but --

DR. MARKS: Okay. Any other comments? If not, then let me see here. Yes, I will be making the motion tomorrow, and it will be a motion to move forward with a "safe conclusion." And it would be a tentative report. Okay. And in the discussion, Ron Shank, if I happen to forget mentioning it, although I shouldn't, would be to discuss the possible ingestion, but the amount is not a toxicologic concern. What's that, Tom?

DR. SLAGA: A five-minute break?

DR. MARKS: Sure. I asked earlier. Sure. Ten- minute break.

DR. SHANK: Whoa.

DR. MARKS: Does that sound good as far as the discussion? Any other discussion points?

DR. SHANK: That sounds good.

DR. MARKS: Okay, good. Thanks, Ron. Thanks, Ron. I have non-irritating aluminum hydroxide at 10 percent.

DR. BELSITO'S TEAM

DR. BELSITO: Okay, so, then we're moving onto alumina and aluminum, is that right?

SPEAKER: Yes.

DR. BELSITO: Okay. So, this is the first time we're looking at this, the bulk of the information. Again, we're taking the approach this has been looked at by FDA for use in medical devices and in antacids and has hydroxide gel for skin-protecting drug products.

So, really, our major issue is going to be sensitization and irritation when it's put on the skin and not so much systemic toxicities given the assumption that's what's out there on the market for cosmetic use is going to be pretty much what is out there for medical use. So, I thought this was safe as used and open it up to my colleagues for their comments.

DR. LIEBLER: So, I basically agree. Ihad in addition to some editorial comments I did have on page 11 of the PDF under "color additives," there's a discussion of the he lakes and colors and then there's an accompanying table that I'm not sure that that's really, really necessary.

SPEAKER: Part or all or --

DR. LIEBLER: So, for example, under "color additives," you've got the first sentence and perhaps the second sentence and that's it, that just describes a non-cosmetic use and then the rest of the paragraph that begins with "All lakes are subject to certification," and then you go on about that, I don't think that stuff's really necessary for this, nor is the accompany table at the end of the report.

MS. BECKER: And just when I was going through all this, I really needed to understand that to understand the rest of it.

DR. LIEBLER: Okay.

MS. BECKER: So, there may be now that it's been distilled out --

DR. LIEBLER: Right, yes. Once you've been through it, you realize okay, it doesn't really need to be there.

DR. BELSITO: So, I'm not clear, Dan. Are you suggesting that all of the information about aluminum lakes

as color additives be deleted or that --

DR. LIEBLER: No, you can simply state -- in that paragraph, colors that contain alumina, blah, blah, are approved by the FDA to be used to color cosmetics, blah, blah, blah. These colors are created by applying color to an alumina substrate, period. You can leave out the rest of that paragraph.

DR. BELSITO: And not refer to the table 2 or --

DR. LIEBLER: Correct.

DR. BELSITO: So, get rid of --

DR. LIEBLER: Table 8, I think it is.

MS. BECKER: Table 5.

DR. LIEBLER: Table 5, sorry.

MS. BECKER: Table 5.

DR. LIEBLER: Thank you, Table 5, yes. And I wouldn't get rid of Table 5, that's the use concentrations. The text is incorrect. Okay, get rid of the table that's not necessary. It's Table 8. Table 8.

DR. BELSITO: Right.

DR. LIEBLER: Yes.

DR. BELSITO: Okay, so, I guess the point here is that we're really not looking at the safety of these lakes, which will be more derived by FD&C dyes.

DR. LIEBLER: I just didn't think that much detail in a non-cosmetic use application was necessary for this report.

DR. BELSITO: Well, I guess the question is: Then do we add them at all because -- so, color additives, colors that -- I guess so this is alumina in medical devices. Okay, fine, I --

DR. BERGFELD: Could I ask a question on the chemistry? I'm not sure what page that is, but at the top after introduction, the chemistry that it talks about, the constituents of emerald, ruby, sapphire, the colors of which come from small impurities of heavy metals within this aluminum oxide. I mean, if you have color being mentioned here, do you think you have to add color --

DR. LIEBLER: Well, those are the reasons that the alumina forms that are mentioned have colors. Those are there in nature, whereas these color additives are manufactured. So, that's the distinction.

DR. BERGFELD: But you aren't suggesting that a paragraph be added to the context regarding those lakes of color be added.

DR. LIEBLER: No.

DR. BELSITO: No.

DR. LIEBLER: Deleted.

DR. BELSITO: Delete. Delete. It's --

DR. BERGFELD: Deleting the table, but are you --

DR. LIEBLER: It's just too much --

DR. BERGFELD: -- deleting the fact that that occurs and mention that --

DR. BELSITO: No, we're just mentioning that it is FDA-approved use --

DR. BERGFELD: Okay.

DR. BELSITO: -- to add these dyes to the alumina lakes.

DR. BERGFELD: Okay, so, there is some mention of that --

DR. LIEBLER: Yes, but that paragraph gives a lot more information about the lakes --

DR. BERGFELD: No, I understand.

DR. LIEBLER: -- that is necessary, so, that's the part that I suggested be deleted.

DR. BELSITO: And then all of Table 8, simply that FDA has said you can add an FD&C dye to aluminum and it's okay.

DR. LIEBLER: Right.

DR. BERGFELD: Could I ask a question of Don. In the physical chemical properties, trace amounts of chromium and cobalt, does that suggest any problem with contact dermatitis?

DR. BELSITO: No, I mean, I think that when you look at the data for aluminum, Finn Chambers are aluminum and most people are reacting to them and then these amounts are being further diluted in formulation. So, I didn't really have an issue with the impurities or really much of anything here.

I had one question here on oral exposure. It said on page 12 of the report, under oral animal for aluminum hydroxide, it said "n equals 7, 8." Was it seven or eight?

MS. BECKER: The groups had seven or eight animals in them, not one or the other. Some had seven, some had eight.

DR. BELSITO: Okay, so, could we put seven or eight because the comma -- and then I had some typographical comments, but otherwise nothing else.

DR. LIEBLER: So, Lillian, I had one other thing. Under the toxicokinetics section on page 11, it says "Overview." PDF page 11, right. It begins with "Most available toxicokinetic and toxicity data are based on aluminum."

So, I think aluminum is distinct from alumina and a data on aluminum are not really relevant. It's like when we had tin and tin oxide. And, so, I think we need to scrub out the aluminum or the discussion of aluminum as opposed to alumina or aluminum hydroxide.

MS. BECKER: What the studies did is they were talking about what aluminum does and they applied the aluminum to the subjects by antacid tablets using aluminum hydroxide.

DR. LIEBLER: So, that's fine.

MS. BECKER: Yes.

DR. LIEBLER: Then that's actually not a study of aluminum.

MS. BECKER: Right, but that's --

DR. LIEBLER: It's a study of aluminum hydroxide. So, we just need to if there are any -- I couldn't tell in a couple of cases if what was studied was aluminum or aluminum hydroxide or alumina. And if there's anything involving just aluminum metal, obviously not applicable to us.

MS. BECKER: Yes.

DR. LIEBLER: And I made a couple of notes here and edits to try and clarify what I think were either -- well, to point out where I thought it might be referring to aluminum as opposed to alumina or aluminum hydroxide. I just want to make sure that we're referring -- I think data on aluminum metal is not relevant.

MS. BECKER: Right.

DR. LIEBLER: Yes.

MS. BECKER: Any of those that are just aluminum, it was the ones that are saying they were studying aluminum, but they were using aluminum hydroxide to do the study.

DR. LIEBLER: Right, so, we should just --

MS. BECKER: I was trying to avert the question as to why does the title say "Aluminum" when you looked at the references.

DR. LIEBLER: Right, so, we shouldn't perpetuate that confusion, we'll just refer to it by the chemical that was studied.

MS. BECKER: Okay.

MS. WEINTRAUB: This may have just been answered by the distinction between alumina and aluminum, but when you think about alumina or perhaps it's aluminum, there is a concern amongst consumers about possibly a link to Alzheimer's. And there's absolutely no mention of that in this report.

I don't know what the scientific sort of broad consensus is on this, but when you do discuss this, and it comes up all the time that people have a concern that there is a link. So, I don't know if that's linked to aluminum and not alumina or if scientifically there is consensus that that is not the case, but I was wondering what the panel thought about address it in some way because reviewing it, its absence was noted.

SPEAKER: Okay.

DR. BELSITO: And it had to do with a concern about aluminum coming from dialysis units I think was the original --

MS. WEINTRAUB: And also deodorants.

DR. BELSITO: Well, deodorants we'll get to in a moment.

MS. WEINTRAUB: Yes.

DR. BELSITO: That wasn't Alzheimer's.

MS. WEINTRAUB: Yes, and like using tin pans, too.

DR. BELSITO: And Alzheimer's and that's been discounted and then the aluminum in deodorants was a different issue. That was breast cancer.

SPEAKER: Also --

MS. WEINTRAUB: Also Alzheimer's.

DR. BELSITO: Alzheimer's.

SPEAKER: Yes.

MS. WEINTRAUB: And, I mean, the relevance to this in particular in my mind was deodorants, but it comes up. So, proving a negative I think is complicated, but I just wanted to point out it seems like an absence.

DR. ANDERSEN: Right, I think you make a good point, Rachel, the idea that a reader should be crystal-clear that this is not a review of aluminum. And the chemistry section makes it clear that we're talking about aluminum oxide and aluminum hydroxide, but why not add a sentence to the introduction that makes it clear that this is not aluminum all by itself?

MS. BECKER: I can do the same thing we did with silica, where differentiating between crystalline and amorphous silica, just making sure it's upfront. We're not talking about that. Don't worry about it.

DR. LIEBLER: That's all fine, but Rachel's concern is a different issue, it's the buzz about "aluminum and Alzheimer's," and I couldn't comment on it directly, I've heard of it, I've followed it. It sounds like something that's been around for a while in terms of the buzz.

DR. BERGFELD: Twenty years of at least.

DR. LIEBLER: So, there ought to be some literature, perhaps a couple of literature reviews that provide some perspective that we could cite perhaps in the discussion.

DR. BERGFELD: Do you want to give it that much emphasis?

DR. LIEBLER: Well, we could look at it.

DR. BELSITO: My only concern is that how do we wordsmith because the fact of the matter is that when looked at scientifically, this has not been considered a concern. So, to disparage an ingredient that we're not looking at to try and say that we don't have concerns with ingredients that we're looking at I think is a very tricky situation.

So, I mean, I understand your point and it's a really valid point because an average reader may look at this and go whoa, these guys didn't even look at Alzheimer's Disease. So, I think that it probably is wise not so much in the introduction, but perhaps in the discussion to say that the panel is aware of concern about the public regarding a potential link between Alzheimer's and aluminum, which has not been validated scientifically. However, it is important to be aware that the ingredients being evaluated here are (inaudible) and not aluminum.

MS. WEINTRAUB: Right. And I realize the complexity and I even raised that in the question, but I wonder if it could even be dealt with in a footnote, as well. We don't usually -- I feel like there are always footnotes in the text. We tend not to talk about them extensively, but I think acknowledging it in the way that you did I think would address that issue.

DR. LIEBLER: Since this is at an early stage, why don't we do this? Why don't we gather a few references that discuss the state of the literature on that and make a little section called neurotoxicity or just neurotoxicity and put it right before repro and developmental in the report and then we'll have it there and the next time we talk about this, we can decide what we want to do with it.

DR. BELSITO: We're going final there. We're going to talk about it when it's done.

DR. SNYDER: I think we can just put it in the introductory saying this is not a safety assessment of aluminum, which has been reported to potentially have -- I mean, I think we could do it there because we've done it before where we say that this is not a safety assessment of something that may be confused or --

DR. BELSITO: In the introduction.

DR. SNYDER: Yes.

DR. BELSITO: I don't care where you put it, but then I think you need to be very careful to craft it and not to implicate aluminum --

DR. SNYDER: Agreed.

DR. BELSITO: -- and Alzheimer's because I think that's pretty much been discounted.

MS. BECKER: Right. Well, as in the silica report, we just made emphasis that we are not discussing crystalline silicon at all.

DR. SNYDER: Yes.

MS. BECKER: It just doesn't refer to it. Yes.

DR. BELSITO: Well, again, I think Rachel's point is the mere fact that aluminum hydroxide, the average consumer isn't going to understand the difference.

DR. LIEBLER: Right, it's not a chemical distinction and, in fact, the concern might have been about, as Rachel said, everything from fry pans to deodorants. Okay, that's the metal and the oxide that covers the span. So, I think a more general couple of citations on the literature and that could be dealt with in the discussion, just as Don said earlier.

DR. BERGFELD: You can't put a reference on the discussion though.

DR. BELSITO: No, but what Dan is saying --

DR. LIEBLER: I suggested that also the section --

DR. BELSITO: -- is just put a section called neurotoxicity before we repro toxicity?

DR. LIEBLER: Right.

SPEAKER: Yes.

DR. BELSITO: Where you put it, Dan?

DR. LIEBLER: Somewhere in that neighborhood.

SPEAKER: Somewhere.

DR. BERGFELD: But you could do what's been suggested in the introductory remarks of what it is not and then footnote it.

DR. LIEBLER: Right, anyplace you can put a citation or two. Better to put a citation or two than to appear to be just blowing it off. That's all.

DR. BELSITO: So, are we going to do a neurotox section, are awe not?

DR. LIEBLER: The winds are shifting. (Laughter) But why don't we just put it in the introduction without a special section and a couple of references? And that'll --

DR. BERGFELD: In a footnote or just a reference?

DR. LIEBLER: On a footnote or just reference this.

DR. BERGFELD: Okay, all right.

DR. KLAASEN: I think we have to look a little bit on what data is there. It's my recollection that if you give "aluminum in some form," and I don't know what it was, to animals, you will get neurofibrils. And which structurally looks like Alzheimer's Disease and I don't know exactly what form of aluminum were used and it was really aluminum or aluminum hydroxide or what was done in those studies, but I think writing this little paragraph would help us all. In the end, we might cross it out, but I think we need to be educated to make sure that we're not saying something wrong.

DR. BELSITO: Okay.

DR. LIEBLER: So, is it premature to make this go final?

DR. BELSITO: I think we can make it go --

MS. BECKER: I think it's a --

DR. BELSITO: No, why?

MS. BECKER: It's a draft report.

DR. BELSITO: Make it go final. It's editorial and we can always decide to --

MS. BECKER: It's a draft.

DR. BELSITO: Tentative final.

MS. BECKER: Yes. It's a draft report.

DR. BELSITO: Yes, well, that's what I mean.

DR. LIEBLER: Okay, so, we do have a chance to see it again.

DR. BELSITO: Yes.

DR. LIEBLER: So, okay, that clarifies it for me. So, I think we need to just look at basically epidemiology on aluminum and Alzheimer's Disease and any animal studies. Those are the things that would probably need to be referred to to address it adequately.

MS. BECKER: There's also a report or two on cognitive effects of the aluminum hydroxide in this report.

DR. LIEBLER: Where was that?

MS. BECKER: Page 12 of the PDF under oral, nonhuman. Sixty-day study on Long Evans male hooded rats.

DR. BELSITO: No increase in --

DR. LIEBLER: Okay, well, then I can go back to let's have a neurotox section.

DR. BELSITO: Yes.

DR. LIEBLER: Neurotox and Alzheimer's Disease, pull that paragraph out along with the other stuff that you'll pull up and I'll put it right after this section, which would be right before repro and developmental.

DR. BERGFELD: So, your intent is to go a tentative final with the intention of adding this paragraph as it's being developed.

DR. BELSITO: Yes.

DR. BERGFELD: And that'll go out in the 60-day review?

SPEAKER: Yes.

DR. BERGFELD: Okay, so, it'll be written without us seeing it.

DR. BELSITO: No, I mean, it will be written and then we'll wordsmith it and it'll be purely editorial and we'll go from there, but, I mean, I think the important point is none of us are concerned about these ingredients, but I think Rachel has a very valid point that we need to make it clear to the consumer that we did consider this concern and why we are not concerned about what they may perceive.

I like Dan's idea of adding a neurotox section. And I think that's -- at least my recollection of it is it's all been totally discounted, had to do with neurofibrillary tangles that were seen in people with chronic dialysis and Curt's point about some feeding of massive doses of aluminum and --

DR. SNYDER: That comment, sodium aluminate is not included in this report?

DR. ANDERSEN: Good question.

DR. BELSITO: Is it in the dictionary? Did you search for it?

SPEAKER: Good for you.

DR. BELSITO: Carol, Paul has a question.

MS. EISENMANN: Well, I didn't make the decision. I mean, it was originally when they gave it to me, I surveyed two ingredients and they took one out and they added aluminum hydroxide instead. So, I don't know why it was taken out.

MS. BECKER: I don't remember exactly why, but Bart did decide that it was not appropriate.

DR. SNYDER: I couldn't find it, I couldn't find the reasoning in either the minutes or otherwise.

DR. ANDERSEN: Okay, well, we will have to bring Bart's chimes on this during the discussion tomorrow or Lill can catch him later.

DR. BELSITO: And, so, it was aluminum --

DR. ANDERSEN: Sodium aluminate.

DR. BELSITO: Sodium aluminate.

DR. ANDESEN: Arguably should be the sodium salt of alumina.

DR. BELSITO: And there's also aluminum acetate, which is used as a drying agent. It's not used in cosmetics.

DR. ANDERSEN: I have no idea.

DR. BELSITO: Solution is 20 percent aluminum acetate. It's not in the cosmetic dictionary?

MS. BECKER: Aluminum acetate?

DR. BELSITO: Yes.

MS. BECKER: It is.

DR. LIEBLER: I think chemically, it's dissimilar enough. I think (inaudible) 3 plus salt with 3 acetates.

DR. BELSITO: Yes.

DR. LIEBLER: Like aluminum chloride or something, which is chemically dissimilar from these. These are all oxygen-coordinated aluminum.

DR. BELSITO: Okay.

DR. LIEBLER: Which is probably why Bart looked at it and said no.

DR. BELSITO: Okay. And that may be the case with your salt, too. So, will you raise that tomorrow or you want me to raise it?

DR. ANDERSEN: Well, she can find out just talking to Bart I'm pretty sure just prior to the --

DR. BELSITO: Oh, okay.

DR. ANDERSEN: That's fine. If there's --

MS. BECKER: I did ask him previously and I just don't remember --

DR. ANDERSEN: Okay.

MS. BECKER: -- the exact reason, but he did decide it was not appropriate.

DR. BELSITO: Okay. Well, we don't want to do anything inappropriate. Okay, are we done with aluminum, alumina?

DAY TWO

DR. MARKS: So, this also is the first time we've seen this draft safety assessment for alumina and aluminum hydroxide. We moved to issue a tentative safety assessment with a safe conclusion.

DR. BELSITO: Second.

DR. BERGFELD: Any other discussion?

DR. MARKS: Yes. There is possible ingestion of these ingredients because of their use, but we felt that that would be not of toxicologic concern since they're such small amounts.

In the skin, the aluminum hydroxide is not irritating, so there's some question about, as I recall, eyelid application of this ingredient. There's no sensitization data, but these are insoluble. So, we felt we didn't need that.

DR. BERGFELD: Discussion from the Belsito team?

DR. BELSITO: Yeah. We just thought that we needed in the introduction to point out that we are specifically not looking at aluminum. It has had some reports to a link to Alzheimer's disease, and Dan Liebler in particular thought that perhaps we should add a little neurotox section indicating that it's botanic aluminum and not these products we're looking at that caused -- that may be linked to Alzheimer's and other neurotoxic endpoints. But, Dan, I'll let you speak to that.

DR. LIEBLER: Well, this really came from a point raised by Rachel in our discussions that there was -- I think we had all heard about it, but we appreciated Rachel kind of reminding us that there was, I think, probably over 10, 12 years ago considerable interest in the possibility that aluminum and even underarm deodorants that contained aluminum compounds may be associated with neurodegenerative diseases, particularly Alzheimer's disease. And I know that there was a flurry of toxicology studies done, Kurt pointed out, in various rodent models attempting to look at the formation of neuro-fibrolary tangles and precipitates -- after aluminum treatment. So, we felt that we don't want to look like we were completely ignoring this, even though I think sort of the weight of evidence suggests that this really isn't a significant ideological factor in Alzheimer's disease. But, that we could deal with this possibly with a couple succinct literature review citations, and of some citations of the animal work in a neurotox section that would go right before the repro and developmental section. And that would at least show that we've considered that issue, and explain why we feel that that issue's not relevant to safety of these in cosmetic products.

DR. MARKS: Yeah, we didn't have Rachel, but we had Ron Shank. (Laughter) Okay? He brought up the same issues, and Ron, did you have anything more to comment? Because --

DR. SHANK: I thought that we could handle it in the discussion, rather than adding a data section.

DR. LIEBLER: We went around and around with that one, and it landed -- it was either the discussion and the introduction, or with this little neurotox section. You know, I don't think we were absolutely stuck on where it would be, but it should be acknowledged and with a couple of citations.

DR. ANDERSEN: Well, some of us were adamant that something is not going to be introduced first in the document in the Discussion. If I'm going to put a citation in, it's not going to be in the Discussion, it's going to be somewhere up front. Now, that could be the Introduction, in which we would include a citation to suggest that this is not a significant concern, but we have to say something in the body of the report up-front if we're going to talk about it in the discussion.

DR. BERGFELD: Ron Hill?

DR. HILL: Part of our discussion yesterday was that -- excuse me -- was that from alumina, you're not going to get any systemic aluminum, and from aluminum hydroxide in use in personal care products, unless somebody was going to drink lots of mouthwash containing -- I mean, drink -- lots of mouthwash containing aluminum hydroxide, it would be essentially no possibility of absorbing any aluminum in any form.

So I mean, when you eat an antacid that has aluminum hydroxide in it, you can get a small amount of aluminum absorbed by virtue of the conversion in the milieu of the stomach because of the hydrochloric acid. There's no cosmetic use or personal care product use that I can see where you would get any -- so, I think you're right. It has to be mentioned, and I don't think we're done seeing aluminum in Alzheimer's yet, but it's not relevant to these two ingredients, period – as far as I saw it.

DR. BERGFELD: Any other discussion? I hear that we have a neurotox section and mention it in the discussion.

DR. LIEBLER: I think that's where we came out, is sort of satisfying the requirement of having some citation and not just springing it in the discussion.

I think we felt that having some literature citations was far preferred over simply saying we're aware of it but not citing any literature at all.

DR. BERGFELD: So, any other items to discuss? If not, I'm going to call the question. All those in favor of a safe conclusion, please indicate by raising your hand. Thank you.

(Motion approved by show of hands)

DR. BERGFELD: Approved.

Safety Assessment of Alumina and Aluminum Hydroxide as Used in Cosmetics

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The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, 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 and Ivan Boyer, Ph.D. D.A.B.T., Senior Toxicologist.

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ABSTRACT

This is a safety assessment of alumina and aluminum hydroxide as used in cosmetics. Alumina functions as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent. Aluminum hydroxide functions as a buffering agent, corrosion inhibitor, and pH adjuster. The Food and Drug Administration (FDA) evaluated the safe use of alumina in several medical devices, which included the review of human and animal safety data. The information from the FDA evaluation served as a basis for determining the safety of alumina and aluminum hydroxide as used in cosmetics by the Cosmetic Ingredient Review (CIR) Expert Panel. The alumina used in cosmetics is substantially the same as that used in medical devices. This safety assessment does not address aluminum as a cosmetic ingredient. The CIR Expert Panel concluded that alumina and aluminum hydroxide are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This is a tentative report on the safety of alumina and aluminum hydroxide as used in cosmetics. Alumina is reported to function in cosmetics as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent; aluminum hydroxide is reported to function as a buffering agent, corrosion inhibitor, and pH adjuster (Table 1).

These ingredients have been approved by the U. S. Food and Drug Administration (FDA) for various medical devices and over-the-counter (OTC) drug uses. The Cosmetic Ingredient Review (CIR) believes that the cosmetic ingredient alumina is chemically equivalent to the alumina used in medical devices as a device color additive for bone cements and sutures and in the construction of dental and hip implants. The FDA found the information submitted for those medical devices to be adequate and determined that alumina is safe for use in devices that come in contact with soft tissue, bone, and internal organs.

CIR also believes the aluminum hydroxide used in cosmetics is chemically equivalent to that used in OTC drugs. The FDA found the information submitted for those drugs to be adequate to support safe use. Based on the adequacy of those data, the FDA also determined that aluminum hydroxide is generally regarded as safe (GRAS) as a food substance and may be used as an antacid and as a direct food additive.

The evaluation by the FDA, and the data below on aluminum hydroxide, is believed to be sufficient for an evaluation of safety of alumina and aluminum hydroxide. Although there is a large amount of data on these ingredients in the literature, relying on the FDA safety assessments makes the need to duplicate that data in the review of these ingredients unnecessary.

CIR has reviewed several cosmetic ingredients that contain an aluminum component (Table 2). All are safe as used.

NOTE: The cosmetic ingredient alumina is not the same as the element aluminum. There have been substantial discussions in the literature about speculation that exposure to elemental aluminum or aluminum compounds could be associated with Alzheimer's disease, breast cancer, and other health issues. Extensive research has failed to support such associations. Furthermore, systemic exposure to aluminum from cosmetic use of alumina and aluminum hydroxide is expected to be negligible. A brief overview of aluminum toxicity is provided below, reflecting the CIR Expert Panel's (Panel) consideration of these issues.

CHEMISTRY

Overview

Definitions, CAS Nos., and functions are provided in Table 1. The structures of alumina and aluminum hydroxide are provided in Figure 1.

Alumina, also known as aluminum oxide (Al_2O_3), is dehydrated (or calcined) aluminum hydroxide.[1] Alumina is also the primary constituent of emerald, ruby, and sapphire (the colors of which come from small impurities of heavy metals). The most common naturally occurring form of alumina is corundum. Corundum is primarily composed of α-alumina, which is crystalline and is the most common phase of naturally occurring alumina. This water-insoluble, inorganic solid can form a number of other crystalline phases, and an amorphous form as well. Each phase has a unique crystal structure and varies in chemical properties, such as its acid-base reaction rate. When synthetically dehydrated from aluminum hydroxide, a mixture of alumina phases typically forms, unless specific controls are applied. While Figure 1 schematically depicts both amorphic and crystalline alumina, data on which form(s) is (are) used in cosmetics were not available.

Aluminum hydroxide, also known as hydrated alumina, is most commonly found as the polymorphid mineral gibbsite (a component of the aluminum ore known as bauxite).[1,2] This inorganic, amphoteric solid, can also form three other polymorphs. However, the chemical formula of $Al(OH)_3$ is the same for all polymorphs, each of which differs from the others only by interlayer spacing and, consequently, by relative acid/base reaction rates.

There are four known polymorphs of crystalline aluminum hydroxide: gibbsite, bayerite, nordstrandite, and doyleite, which can have different chemical/physical properties.[3] The properties of the starting materials (pH, presence of anions or salt, and mineral surfaces) are what influence the formation of particular polymorphs from aluminum interlayers and/or hydroxyl-aluminum polymers. All the polymorphs of aluminum hydroxide consist of layers of aluminum octahedra with hydroxyl groups on either side that hydrogen bond the layers together, and differences arising from variations in the

stacking sequences of the layers. Of the possible configurations, gibbsite and bayerite represent the two ends of the spectrum of types of stacking sequences. Nordstrandite and doyleite have intermediate structures.

There is no universal standard nomenclature for aluminum oxides and hydroxides; thus, there may be inconsistencies in the use of these names among sources.[3] Categorization is based on crystallographic structures found under environmental conditions and cited most often in the literature (Table 3). The α prefix is generally applied to hexagonal close-packed and related structures; these are aluminum minerals abundantly found in nature. The γ prefix is generally applied to designate polymorphism, structural alteration, or dehydration of these minerals (originally applied to all aluminum hydroxides and hydrolyzed aluminas other than the α-phase minerals). The γ-phase has cubic close-packed lattices or related structures.

Physical and Chemical Properties

Alumina and aluminum hydroxide are white, insoluble solids (Table 4). Alumina is the third hardest naturally occurring substance after diamond and carborundum (SiC).[4] The presence of trace amounts of chromium or cobalt creates ruby and sapphire, respectively.

Aluminum compounds cannot easily be oxidized, and thus atmospheric transformations generally are not expected to occur.[5]

All forms of aluminum hydroxide are amphoteric (e.g., they can act as both acids and bases in solution).[6] Accordingly, aluminum hydroxides can act as buffers to resist pH changes within the narrow pH range of 4–5.[7] Aqueous aluminum hydroxide gel has an effective pH of ~6.[8]

Method of Manufacture

Aluminum hydroxide is most commonly produced by aqueous alkaline extraction from bauxite ore, a method known as the Bayer process.[1] Alumina is then produced from the resultant aluminum hydroxide simply by vigorous heating to drive off water.[9]

Impurities

Alumina balls used in artificial hips must meet the following specifications: grain size < 5 microns and purity > 99.7% aluminum oxide.[10] The maximum percentages for trace substances permitted are: MgO, 0.2%; SiO_2, 0.01%; CaO, 0.03%; Na_2O, 0.02%; Fe_2O_3, 0.03%, and TiO_2, 0.01%.

When used in OTC drugs as a color additive, alumina should contain no more than 0.5% insoluble matter in dilute hydrochloric acid. The following are the limits of impurities: lead (as Pb) ≤ 10 ppm, arsenic (as As) ≤ 1 ppm, mercury (as Hg) ≤ 1 ppm, and aluminum oxide (Al_2O_3) ≥ 50% (21CFR 73.1010)

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 5).[11] A survey has been conducted by the Personal Care Products Council (Council) of the maximum use concentrations.[12,13]

Alumina was reported to be used in 523 leave-on products at concentrations up to 60% (in nail products). It is reported to be used in 40 rinse-off products. Formulations include 84 products used around the eye at concentrations up to 30%, 87 lipsticks up to 6.7%, and 104 skin care preparations up to 25%.

Aluminum hydroxide was reported to be used in 572 leave-on products up to 10.1% and 6 rinse-off products up to 8.8%. Formulations include 80 products used around the eye up to 10.1%, 154 lipsticks up to 7%, oral hygiene products up to 8.8%, and 6 suntan preparations up to 0.9%.

Non-Cosmetic

Aluminum salts are incorporated into some vaccine formulations as an adjuvant to enhance the immune response to vaccination.[14] The aluminum compounds used in some U.S. licensed vaccines are aluminum hydroxide, aluminum phosphate, alum (potassium aluminum sulfate), or mixed aluminum salts. Aluminum hydroxide may be used in vaccines up to 25 µg/L in large-volume parenteral drug products (21 CFR 201.323) and up to 1.25 µg/single dose, depending on calculation method (Table 6; 21 CFR 610.15).

The FDA evaluated the safety of aluminum hydroxide in OTC drugs (Table 6). The FDA stated that the oral maximum daily dose of an antacid containing aluminum hydroxide dried gel is 8 g (21 CFR 331.11). A chewable tablet of aluminum hydroxide:magnesium trisilicate (80:20 mg) was approved by FDA.[15] Two other chewable tablets were approved with aluminum hydroxide:magnesium trisilicate doses of 80:20 mg and 160:40 mg.[16] Liquid suspensions of aluminum hydroxide are also used as antacids.[17]

Aluminum hydroxide gel is approved for use in OTC skin protectant drug products as an active ingredient at 0.15% - 5%, with caution to consult a doctor for children under 6 months (Table 6) (21 CFR 247.10; 21 CFR 347.50).

The safety and effectiveness of aluminum hydroxide for use in OTC drugs has not been established for the treatment

of diarrhea or the topical treatment of acne. Aluminum hydroxide has been approved for use in digestive aid drug products and preparations for treating diaper rash (21 CFR 310.545).

Alumina is used as an adsorbent, desiccant, and abrasive.[18] It is used as filler for paints and varnishes. It is also used in the manufacture of alloys, ceramic materials, electrical insulators and resistors, dental cements, glass, steel, and artificial gems. It is used in coatings for metals and other surfaces and as a catalyst or catalyst substrate for organic chemical reactions.

Aluminum hydroxide is considered GRAS as a food ingredient by the FDA.[19]

The National Institute for Occupational Safety and Health placed a limit for α-alumina of 15 mg/m^3 total time-weighted average exposure in workplace air and 5 mg/m^3 in the respirable fraction.[20]

There are many regulations for aluminum or other aluminum compounds. Those that are informative for the purpose of this safety assessment are listed in Table 7.

ALUMINA IN MEDICAL DEVICES

Alumina has been approved by the FDA for use in medical devices. The alumina used in these devices must comply with ASTMF603-12, "Standard Specification for High-Purity Dense Aluminum Oxide for Medical application".[21]

The FDA considered the safety of alumina when approving the following medical devices that contain this material:

- Color additive for polymethyl methacrylate (PMMA) bone cement and sutures,
- Endosseous dental implant abutments, and
- Femoral bearing head of artificial hips.

Color Additives

Colors that contain alumina (i.e., FD&C Blue #1 Aluminum Lake) are approved by the FDA to be used to color cosmetics, food, dietary supplements, drugs for internal and external use, and medical devices (i.e., bone cement, surgical sutures).[22] These colors are created by applying the color to an alumina substrate.

Alumina has been approved as a color additive for OTC drugs (21 CFR 73.1010).

Ceramic Hip

The use of ceramic femoral heads (i.e., Ceramtec™ Alumina Heads, Alumina V40 Head) made of an alumina/ceramic composite have been approved for use on hip joint replacements in humans. The material conforms to FDA's "Guidance document for the preparation of premarket notifications for ceramic ball hip systems".[10,23,24]

One hip replacement product was reported to consist of ~75% alumina, ~25% zirconia, and < 1% chromium oxide.[25]

Other Devices

Alumina has been approved for use in endosseous dental implant abutments (Table 6) (21 CFR 872.3630).

Alumina/ceramic composite is used to make internal stents for treating tracheomalacia.[26] These stents are implanted within the trachea.

TOXICOKINETICS

Overview

The aluminum from aluminum hydroxide is poorly absorbed through either oral or inhalation routes and is essentially not absorbed dermally in healthy humans.[27] Orally, approximately 0.1% – 0.6% of aluminum is usually absorbed; the less bioavailable forms of aluminum hydroxide are absorbed at only approximately 0.1%. Unabsorbed aluminum from ingested aluminum hydroxide is excreted in the feces. The oral bioavailability of aluminum is strongly influenced by the type of aluminum compound and the presence of dietary constituents that can complex with aluminum and thereby enhance or inhibit absorption. The main mechanism of absorption in the gastrointestinal tract is thought to be passive diffusion through paracellular pathways. Absorbed aluminum binds to various ligands in the blood and distributes to every organ, but persists mostly in bone and lung tissues. Absorbed aluminum is excreted mostly in the urine and, to a lesser extent, in the bile. Studies on aluminum uptake and elimination rates, using aluminum hydroxide, indicate that a near steady-state is maintained in most healthy adults, with aluminum body burdens varying slightly up and down over time with an overall small rate of increase over the lifespan. High levels of aluminum, such as those associated with long-term use of antacids, will cause levels to increase in the blood and other tissues. The levels return to normal upon cessation of high-level exposure. Under certain atypical conditions (e.g., poor renal function with increased aluminum load), levels of aluminum in the body may raise high enough to cause toxicity in humans.

Blood and tissue (liver, spleen, kidney, brain, bone) levels of aluminum from the ingestion of aluminum hydroxide (100, 281, 1500, 2000 mg/kg/d) were increased by concurrent oral administration of citric, lactic, malic, oxalic, and tartaric acids in rats.[28-30]

Dermal

Aluminum salts used in antiperspirants form a hydroxide precipitate of denatured keratin in the cornified layer that surrounds and occludes the opening of sweat ducts.[31] The authors concluded that these mechanisms suggest that there is little or no dermal absorption of aluminum hydroxide, or any other form of aluminum.

Oral - Non-Human

ALUMINUM HYDROXIDE

Bioavailability of orally administered [^{26}Al]aluminum hydroxide (in 2 ml water; pH 7) to male Wistar rats (n = 9) was 0.1%.[32] After administration, the rats were placed in metabolic cages and blood sampled at 20, 45, 60, 90, 150, and 300 min. The rats were then killed and necropsied.

The aluminum content returned to normal levels in the tissues of Sprague-Dawley rats within 21 days after oral administration of aluminum hydroxide.[33] In the first study, the rats were fed a control diet containing 26 µg Al/g (n = 5) or 989 µg Al/g (n = 15) for 16 days. All rats were then fed the control diet. Five rats were killed and necropsied at the end of the test period and at 7 and 21 days. The treatment group had increased aluminum in the tibiae-fibulae, ulnae-radii, leg muscles, and kidneys. At day 21, all aluminum content values were similar to controls.

This experiment was repeated with 9 rats (control) and 1070 µg Al /g in the diet, and the rats were killed and necropsied at 0, 3, and 7 days after treatment. The increase in aluminum content in the test group returned to control levels by day 7. Ingestion of aluminum hydroxide had no effect on the levels of phosphorus, calcium, magnesium, zinc, and iron in the tissues examined.

Only 0.45 ± 0.47% of orally administered aluminum hydroxide (10,000 µmol/kg as concentrated aluminum hydroxide gel with 4 ml water by stomach tube) to renally-intact rabbits (n = 10) was absorbed.[34] Renally impaired rabbits absorbed 0.36 ± 0.30%.

Oral - Human

Orally administered aluminum hydroxide is poorly absorbed (at $< 0.01\%$) in humans.[35,36]

Using ^{26}Al, the estimated aluminum absorption rates were 0.523%, 0.0104%, and 0.136% in two subjects receiving a single dose of aluminum citrate, aluminum hydroxide, or aluminum hydroxide dissolved in an aqueous citrate solution, respectively.[37] The test materials were delivered to the stomach through a pediatric feeding tube. Blood was collected at 1, 4, and 14 h. Feces and urine were collected for 6 days. The uptake of aluminum was greatest in the citrate form and least as aluminum hydroxide. The addition of citrate to the aluminum hydroxide increased the ^{26}Al uptake in both subjects.

There was no appreciable increase in the amount of aluminum absorbed in subjects (n = 8, 10, 7) administered aluminum hydroxide (equal to 244, 976, or 1952 mg Al in the form of antacid tablets; pH 9.2).[38] By measuring the amount of aluminum in the urine, the amount of aluminum absorbed was 0.001%, 0.004%, and 0.007%, respectively. When the high dose was combined with orange juice (70 ml; pH 4.2) or citric acid (70 g in 1000 ml distilled water; pH 2.4), absorption increased to 0.03% and 0.2%, respectively.

Intravenous

ALUMINUM HYDROXIDE

The half-life of i.v. administered aluminum hydroxide (100 µmol/kg as concentrated aluminum hydroxide gel) in renally intact rabbits (n = 10) was 27 ± 13 h.[34] In renally-impaired rabbits, the half-life was 14 ± 5 h. Blood was sampled at 24 h and immediately prior to treatment and at ~5, 10, 20, 30, 45, and 60 min and 2, 4, 8, 12, 24, and 48 h after treatment.

TOXICITY

Repeated Dose

Oral – Animal

ALUMINUM HYDROXIDE

When aluminum hydroxide (average 2400 mg/kg/k in drinking water) was administered to Long Evans male hooded rat weanlings (n = 7 or 8) for 60 days, there was no reduction in cognitive abilities.[39] At necropsy, the highest concentration of aluminum in the brain was in the hippocampus. The test group had decreased weight gain compared to controls, possibly reflecting reduced water intake at the beginning of the test period. The rats were assessed with an open field activity test biweekly. At the end of the test period, the rats were tested for muricidal behavior by placing an albino mouse with each of the rats. Only one treated rat exhibited the behavior.

When aluminum hydroxide (300 mg/kg in carboxylmethyl cellulose) and aluminum hydroxide (100 mg/kg) plus citric acid (30 mg/kg) were orally administered to Long Evans rats (n = 10/sex), their learning ability was reduced when measured using a four-T shaped labyrinth.[40] Control rats learned the way to the goal an average of 5.1 ± 2.88 times vs. 16.0 ± 2.98 and 13.2 ± 5.39 times for the two treatment groups, respectively. The amount of aluminum content of the brains of the control rats at necropsy was 6.6 ± 3.01 ppm compared to 18.0 ± 10.20 and 11.0 ± 4.80 ppm in the two treatment groups, respectively. There was also increased acetylcholinesterase activity in the aluminum hydroxide plus citric acid group. There

was no increase in choline-acetyltransferase activity in the brains of either group. No other clinical signs or abnormalities were reported.

Intraperitoneal – Animal

ALUMINUM HYDROXIDE

Male Wistar rats (n = 12) exhibited decreased weight gain and initial feed efficiency when administered i.p. aluminum hydroxide (80 mg/kg) 3 times/week for 6 months.[41] There were no differences in feed intake. Aluminum hydroxide did not affect the peak growth rate or the time to reach maturity. The systemic calcium balance in the treated rats was decreased and there was an increase in the amount of calcium excreted in the feces. The rate of skeletal Ca^{++} accretion was decreased with changes in the bone calcium resorption.

Oral – Human

ALUMINUM HYDROXIDE

There were no adverse effects observed when subjects (n = 9 females, 4 males) were administered aluminum hydroxide (equal to 59 mg Al) three times daily for 6 weeks.[42] When compared to the control group (n = 3 females, 2 males) urinary Al was ~ 10- to 20-fold greater during treatment. The authors state that this indicated that ingestion of an Al-containing antacid is associated with Al absorption above that originating from food and drinking water. There were no differences in the lymphocyte subpopulations, lymphocyte proliferation and *in vitro* Ig and IL production. There were no differences between groups in the immune parameters examined, except for a slightly smaller CD8+CD45R0+ population (primed cytotoxic T-cells) in the test group compared to the referents.

In a report by the Agency for Toxic Substances and Disease Registry, a minimum risk level of 1 mg Al/kg/d was derived for intermediate-duration oral exposure (15 - 364 days) for aluminum and 1 mg Al/kg/d for chronic-duration oral exposure (365 days or longer).[27]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

ALUMINUM HYDROXIDE

When aluminum hydroxide (0, 66.5, 133, or 266 mg/kg in distilled water) was administered by gavage on gestation days 6 – 15 to Swiss mice (n = 20), there were no effects attributed to the test substance.[43] There were no differences in maternal weights, feed consumption, appearance, or behavior. There were no differences in number of total implants, resorptions, number of live or dead fetuses, fetal size parameters, or sex distribution observed at necropsy. There were no differences observed at gross external, soft tissue, and skeletal examinations.

When aluminum hydroxide (384 mg/kg/d; n = 18), aluminum citrate (1064 mg/kg/d; n = 15), or aluminum hydroxide (384 mg/kg/d; n = 19) plus citric acid (62 mg/kg/d) was orally administered to Sprague-Dawley rats (during gestation day 6 – 15), there were no differences among groups in pre- or post-implantation loss, number of live fetuses per litter, or sex ratio.[44] Fetal body weight was reduced and skeletal variations (delayed ossification of occipital bone and sternebrae; absence of xiphoides) were increased in the aluminum hydroxide plus citric acid group. The absence of xiphoides was also observed in the aluminum citrate group. The dams had decreased weight gain in the aluminum hydroxide plus citric acid group during treatment but recovered and caught up to the other groups post treatment. There was increased aluminum in the livers, bones, and placentas of the aluminum citrate group. There were no differences in aluminum content in the kidneys and brains. Aluminum was not detected in whole fetuses. The control group (n = 17) was administered water.

IRRITATION

ALUMINUM HYDROXIDE

Aluminum hydroxide (10% w/v in 0.2% Tween-80) was not irritating when applied to the shaved backs of female TF1 strain albino mice (n = 5; 0.5 ml), New Zealand White rabbits (n = 3; 0.5 ml), and large white strain pigs (n = 2; 1.0 ml) for 5 consecutive days.[45] The test substance was applied uncovered. The animals were restrained until the substance was dry.

CLINICAL USE

Clinical Trials

There are multiple clinical trials of alumina-on-alumina or alumina ceramic hips, alumina/ceramic composite stents, and dental implants. There were no adverse reactions reported. None of the failures reported were attributable to adverse health effects of the alumina but were related to mechanical or implantation technique issues (Table 8).

In a review of four case studies of alumina ceramic hip implant failures, it was determined that all problems were due to design issues, implementation issues, or surgical issues.[46] None of the failures were attributed to adverse reactions to the alumina.

OVERVIEW OF ALUMINUM TOXICITY

ABSORPTION

Aluminum in cosmetics and in antiperspirants is not systemically absorbed to any appreciable extent through the skin.[47-49] Aluminum is poorly absorbed in both the respiratory tract and the gastrointestinal tract.[50]

Gastrointestinal absorption of dietary aluminum generally ranges from 0.01% to 0.6% in humans, although absorption of large bolus doses (up to 0.5 g) of aluminum hydroxide, ingested as antacids throughout the day, and other insoluble aluminum compounds is normally ≤ 0.01%.[35,36,51-60] In contrast, the absorption of water soluble aluminum compounds can range from 0.5 to 5%.[50] Accordingly, dietary constituents can enhance or inhibit aluminum absorption in the digestive tract by forming absorbable, usually water soluble, complexes (e.g., citric, lactic or other carboxylic acids) or by forming un-absorbable, generally insoluble compounds (e.g., phosphate or dissolved silicate).[50,61,62]

OSTEOMALACIA

There are many case reports of osteomalacia in otherwise healthy infants, children and adults after long-term ingestion of aluminum-containing antacids (e.g., aluminum hydroxide given with buffered citrate) for gastrointestinal problems.[50,63-68] The skeletal effects in these cases are attributable to impaired phosphate absorption through the formation of insoluble complexes between aluminum and dietary phosphorous in the gut, which leads to hypophosphatemia and phosphate depletion in the bone.

DIALYSIS ENCEPHALOPATHY

Most human studies on the toxicity of aluminum are reports of osteomalacia, microcytic anemia, and neurological effects in hemodialysis patients suffering from chronic renal failure.[48,50,52,62,67,69-85] Many of these patients developed signs of central nervous system toxicity, sometimes progressing to dialysis-encephalopathy syndrome and even death. These effects are attributable to the accumulation of aluminum in the brain from long-term intravenous hemodialysis with aluminum-contaminated dialysis fluid and, often, concurrent high oral doses of aluminum hydroxide.[50,52,67,86,87] However, these studies have limited usefulness for predicting toxicity in the general population because kidney failure, coupled with very large aluminum exposures, causes atypical aluminum accumulation and risk of aluminum-induced effects in these patients.[50]

ALZHEIMER'S DISEASE

The hypothesis that aluminum could be involved in the pathogenesis of Alzheimer's disease stems from an early report that aluminum was detected in senile plaques and neurofibrillary tangles (NFTs) in brain tissue from Alzheimer's disease patients.[88] Since then, several authors reported increased aluminum concentrations in brain tissue from Alzheimer's disease patients compared to that from adults without Alzheimer's disease.[67,89-93] However, others found no increase in aluminum levels in brain tissues of Alzheimer's disease patients.[67,80,94-97] Further, other researchers found patients with elevated brain aluminum levels but with no clinical signs of Alzheimer's disease.[67,98,99] In a study of brains taken at autopsy (n = 50), signs of dialysis encephalopathy were found in 10 hemodialysis patients with a history of high-dose aluminum ingestion (total doses up to 2478 g), but no evidence of Alzheimer's disease morphology was found in any of them.[100] In contrast, Alzheimer's disease morphology was found in 6 patients who had ingested little or no aluminum-containing drugs. The authors concluded that there was no link between the total amount of ingested, bioavailable aluminum administered medically and the appearance of Alzheimer's disease-associated aluminum inclusions in glial and neuronal cells.

Several epidemiological studies have examined the possible association between Alzheimer's disease and exposure to aluminum in drinking water.[50,101-117] These studies report conflicting results and have been criticized for flawed subject selection, small sample sizes, poor exposure assessment, inaccurate diagnosis of Alzheimer's disease, weak statistical correlations and failure to adjust for important confounding factors.[48,50,52,56,67,118,119]

Other epidemiological studies have associated total dietary aluminum consumption with increased risk of Alzheimer's disease.[67,120] However, no significant association was found between Alzheimer's disease and the ingestion of aluminum from tea (typically 2 to 6 mg/L aluminum, or 10 to 50 times higher than in drinking water).[52,104,120,121] In addition, no significant association was found with the use of antacids (typically 300 to 600 mg aluminum hydroxide per tablet, capsule, or 5 mL liquid dose).[48,50,67,104,122-127] Likewise, no significant association was found between Alzheimer's disease and inhalation exposure to aluminum dusts and fumes in the workplace.[50,67,128-131]

Overall, the available studies have not substantiated a causal link between aluminum exposure and Alzheimer's disease, and the role it may play, if any, in the development of this disease remains to be determined.[50,52,56,67,132-138]

BREAST CANCER

Alumina and aluminum hydroxide as used in cosmetics are not approved active ingredients in antiperspirant products in the U.S. (21 CFR 68.110)

Aluminum chloride (anhydrous), aluminum chlorohydrate, and aluminum hydroxide (alumina trihydrate) are commonly used as the active ingredient in underarm antiperspirant products.[50,139-142] Aluminum chloride, aluminum chlorhydrate and aluminum zirconium chlorohydrate glycine have been used in antiperspirant products at up to 15%, 20% and 25% by weight, respectively.[143,144] Darbre has suggested that long-term, regular underarm and breast-area application of

products containing potential endocrine disruptors may promote the development of breast cancer.[143-148] Further, this author has suggested that aluminum chloride and aluminum chlorohydrate have the potential to disrupt endocrine function in human breast cancer cells by interfering with the binding of estrogens to estrogen receptors and inducing estrogen-regulated gene expression, based on the results of in vitro experiments using the estrogen-sensitive MCF-7 breast cancer cell line.[143,144,147]

Specifically, aluminum chloride at $\geq 2.5 \times 10^{6}$ molar excess (compared to the estradiol concentration), or aluminum chlorhydrate at $\geq 5.0 \times 10^{6}$ molar excess inhibited [^{3}H]estradiol binding by $\geq 40\%$ ($p \leq 0.005$) or $\geq 64\%$ ($p < 0.001$), respectively.[143,144] Pre-incubation of MCF-7 cells with $\geq 10^{-3}$ M aluminum chloride or $\geq 3 \times 10^{-4}$ M aluminum chlorohydrate for 14 days inhibited the estrogen-stimulated growth of the cells ($p \leq 0.002$), which the author suggests indicates the resilience of MCF-7 cells to relatively high concentrations of these aluminum compounds. Further, incubation with 10^{-4} M aluminum chloride or aluminum chlorhydrate for 8 days induced the activity of a stably transfected estrogen-responsive chloramphenicol acetyl transferase (CAT) reporter gene in MCF-7 cells, whether or not estradiol was added during the final day of the incubation period ($p \leq 0.023$).

The results of these experiments indicate that aluminum compounds, particularly water-soluble aluminum compounds, at relatively high concentrations can perturb estrogen receptor-mediated activities in MCF-7 breast cancer cells incubated in vitro long enough and at sufficiently high concentrations. However, these observations are not relevant to the use of alumina and aluminum hydroxide, which are insoluble and are not absorbed through the skin to any significant extent, in cosmetics.

Furthermore, there were no association between underarm antiperspirant or deodorant use and breast cancer in a population-based case-controlled epidemiological study conducted in the U.S.[149] Briefly, breast cancer patients (n = 813) were compared with control subjects (n = 793) from the same population, which were frequency matched to the cancer patient by 5-year age groups. Measures of antiperspirant or deodorant use included self-reported ever regular use, exclusive of antiperspirant versus deodorant (or vice versa), and regular use with in 1h of underarm shaving. Odds ratios ranged from 0.9 – 1.2 and p values from 0.12 – 0.40. The assessment of both antiperspirant and deodorant use in this study helped address the possibility that some of the subjects may have reported deodorant use when they actually used an antiperspirant (or vice versa), or may have used a combination of the two.

Overall, the scientific literature provides no plausible evidence linking breast cancer to the use of under antiperspirant or deodorant products.[150]

SUMMARY

Alumina functions in cosmetics as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent; aluminum hydroxide functions as a buffering agent, corrosion inhibitor, and pH adjuster.

CIR considers that the alumina and aluminum hydroxide produced for cosmetics to be chemically equivalent to the materials used to color surgical sutures and in other commercial medical devices made of alumina as well as that used in OTC drugs and vaccines. The safety information for those medical devices and drugs was provided to the FDA in medical device and drug applications including the results of: acute and long-term biocompatibility testing for cytotoxicity, irritation or intracutaneous reactivity, sensitization, systemic toxicity, implantation effects, and hematocompatibility studies. The FDA found those data to be adequate and determined that alumina was safe and effective for use in hip and dental implants as well as for coloring PMMA bone cement and surgical sutures. Aluminum hydroxide is GRAS as a food additive and safe in OTC drugs and vaccines.

Alumina was reported to be used in 523 leave-on products at concentrations up to 60% (in nail products). It is reported to be used in 40 rinse-off products up to 25%. Aluminum hydroxide was reported to be used in 572 leave-on products up to 10.1% (in eye products) and 6 rinse-off products up to 8.8% (in oral hygiene products).

Alumina is used in color additives for sutures, endosseous dental implant abutments, and femoral bearing head of artificial hips.

In clinical trials of artificial hips, dental implants, and esophageal stents, all adverse effects were from mechanical or installation problems, not due to exposure to alumina.

Orally administered aluminum in aluminum hydroxide has low bioavailability and is excreted primarily in the feces; the absorbed aluminum is excreted primarily in the urine.

Aluminum hydroxide orally administered to rats at 2400 mg/kg had no effect on cognitive abilities but when 100 mg/kg was administered to rats with citric acid, reduced learning ability was demonstrated.

Rats exhibited decreased weight gain and initial feed efficiency when administered i.p. aluminum hydroxide at 80 mg/kg 3 times/week for 6 months.

There were no effects to immunity parameters in humans orally administered aluminum hydroxide (equal to 59 mg Al) three times daily for 6 weeks.

There were no reproductive effects in mice when orally administered aluminum hydroxide at 266 mg/kg during gestation days 6 – 15 or to rats at 384 mg/kg. However, when administered with citric acid, there was reduced weight gain in the dams and an increase in skeletal abnormalities in the pups.

Aluminum hydroxide at 10% was not dermally irritating to mice, rabbits, and pigs (n = 2; 1.0 ml).

DISCUSSION

The CIR Expert Panel emphasized that this is a safety assessment of alumina and aluminum hydroxide and that these ingredients are not to be confused with elemental aluminum. The Panel notes that the scientific literature provides no plausible evidence linking breast cancer or Alzheimer's disease to products that contain aluminum. The FDA requires a warning on injections that contain aluminum (Table 6). This rule refers to the large volumes of injected aluminum which does not relate to the dermally applied ingredients in this report.

The Panel was not concerned with the potential for incidental ingestion of alumina when used in lipsticks or oral hygiene formulations. The amounts of aluminum ion that would be released in the digestive tract are well below the levels of toxicological concern.

Since these ingredients are practically insoluble and are not dermal irritants, there was no concern about dermal penetration or cosmetic application around the eye.

The Panel discussed the issue of incidental inhalation exposure from powders and fragrance preparations. There were no inhalation toxicity data available. The Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics.

These ingredients are reportedly used at concentrations up to 6% in cosmetic products that may be sprayed and up to 5% in other products that may become airborne. The Panel noted that 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for alumina and aluminum hydroxide to cause dermal irritation and systemic toxicity in multiple clinical trials of medical devices consisting of alumina. Alumina and aluminum hydroxide are insoluble in water thus not systemically toxic. 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 alumina and aluminum hydroxide are safe in the present practices of use and concentration described in this safety assessment.

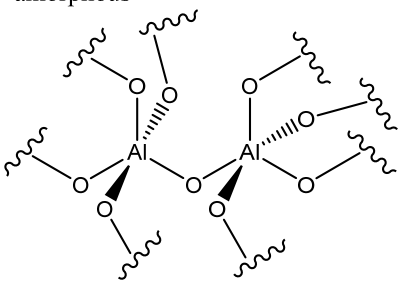
TABLES AND FIGURES

Figure 1. Formulas and idealized structures of the ingredients in this safety assessment.

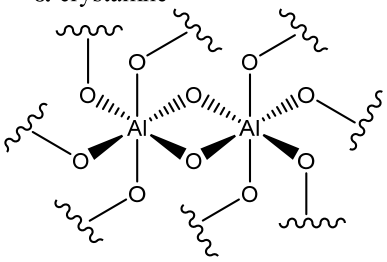
Alumina

aluminum oxide

amorphous



α-crystalline



Aluminum hydroxide

aluminum hydroxide

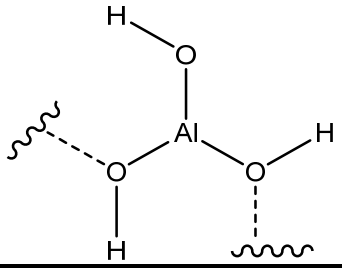


Table 1. Definitions and functions of the ingredients in this safety assessment.[151]
(The *italicized* text below represents additions made by CIR staff.)

Ingredient CAS No.	Definition	Function
Alumina 1333-84-2 (hydrate *("hydrate" in reference to Alumina often means Aluminum Hydroxide or something between Alumina and Aluminum Hydroxide); alternative CAS No. for 21645-51-2*) 1344-28-1	Alumina is an inorganic compound that conforms to the formula: Al_2O_3. *Aluminum oxide, also known as Alumina, is a mineral found as corundum, emery, ruby, sapphire, and in hydrated form (i.e., aluminum hydroxide) as bauxite or gibbsite.*	Abrasive, absorbent, anticaking agent, bulking agent, opacifying agent
Aluminum hydroxide 1333-84-2 21645-51-2	Aluminum hydroxide is an inorganic compound that conforms to the formula $Al(OH)_3 \cdot xH_2O$. *Alumina hydrates are true hydroxides (meaning they do not contain water of hydration; they are often called hydrated alumina or aluminum hydroxide) and are naturally occurring as minerals including bauxite or gibbsite.*	Opacifying agent, skin protectant

Table 2. Cosmetic ingredients containing aluminum that have been reviewed by CIR.

Ingredients	Conclusion	Maximum concentration (%)	Reference
Alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicate, Sodium potassium aluminum silicate	Safe as used when formulated to be non-respirable.	44	152
Aluminum citrate	Safe as used.	80	153
Aluminum dimyristate, aluminum isostearates/myristates, aluminum myristate, aluminum myristates/palmitates	Safe as used.	82	154,155
Aluminum silicate, magnesium aluminum silicate	Safe as used.	100	156
Aluminum starch octenylsuccinate	Safe as used with limitations on heavy metal content	30	157
Aluminum distearate, aluminum stearate, aluminum tristearate	Safe as used.	25	158,159
Calcium aluminum borosilicate	Safe as used.	97	160
Potassium aluminum polyacrylate	Safe as used when formulated to be nonirritating	25	161

Table 3. Comparison of nomenclatures for alumina and aluminum hydroxide.[3]

Mineral Name	Chemical composition	Common crystallographic designation	Past accepted crystallographic designation
Gibbsite (hydrargillite[1])[2]	Aluminum trihydroxide	α-$Al(OH)_3$	γ-$Al(OH)_3$
Bayerite	Aluminum trihydroxide	β-$Al(OH)_3$	α-$Al(OH)_3$
Nordstrandite	Aluminum trihydroxide	$Al(OH)_3$	$Al(OH)_3$
Doyleite	Aluminum trihydroxide	$Al(OH)_3$	-
Boehmite	Aluminum oxyhydroxide	γ-AlOOH	γ-AlOOH
Diaspore	Aluminum oxyhydroxide	α-AlOOH	α-AlOOH
Corundum (α-alumina)	Aluminum oxide	α-Al_2O_3	α-Al_2O_3

[1] Hydrargillite is a mineral that was named after the Greek hyder (water) and argylles (clay). The name hydrargillite was mistakenly given to describe aluminum hydroxide, but later was proven to be aluminum phosphate. However, both names are still used to describe aluminum hydroxide: gibbsite is preferred in the United States and hydrargillite is used more often in Europe.
[2] The terms in parenthesis refer to possible forms.

Table 4. Chemical and physical properties of alumina and aluminum hydroxide.

Property	Value	Reference
Alumina		
Physical form	Solid, crystalline powder	18,162
Color	White	18
Odor	None	162
Gram formula weight g/mol	101.96	18
Density/specific gravity @ 20ºC	4.0	18
Viscosity kg/(s·m)@ 20ºC	Solid	162
Vapor pressure mmHg@ 20ºC	Negligible	162
Melting point ºC	~2000	18
Boiling point ºC	2980	18
Water solubility	Insoluble	18
Aluminum hydroxide		
Physical form	Amorphous powder	18
Color	White	18
Gram formula weight g/mol	78.00	18
Density/specific gravity	2.42	18
Melting point ºC	300	18
Water solubility	Practically insoluble	18

Table 5. Frequency of use according to duration and exposure of alumina and aluminum hydroxide.[11-13]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Alumina		Aluminum hydroxide	
Total/range	**563**	**0.0004-60**	**578**	**0.0000008-10.1**
Duration of use				
Leave-on	523	0.0004-60	572	0.0000008-10.1
Rinse-off	40	0.003-25	6	NS0.0022-8.8
Diluted for (bath) use	NR	NR	NR	NR
Exposure type				
Eye area	84	0.00075-30	80	0.009-10.1
Incidental ingestion	88	0.0004-6.7	155	0.0022-8.8
Incidental Inhalation-sprays	7	6	6	NR[a]
Incidental inhalation-powders	41	0.0023-5	40	0.029-1.5
Dermal contact	441	0.0023-30	409	0.0000008-10.1
Deodorant (underarm)	NR	0.004-0.01	NR	NR
Hair-noncoloring	1	NR	NR	0.004-0.016
Hair-coloring	NR	1	NR	0.1
Nail	30	0.0048-60	7	0.016-1
Mucous Membrane	107	0.0004-6.7	157	0.0022-8.8
Baby	NR	0.0023	NR	NR

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

[a] The Council reports that the skin care preparations and suntan preparations in their survey are not sprays.

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.

Table 6. United States government regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

Device/Drug	Rule	Reference
Endosseous dental implant abutment		
	An endosseous dental implant abutment [made of alumina] is a premanufactured prosthetic component directly connected to the endosseous dental implant and is intended for use as an aid in prosthetic rehabilitation. Class II (special controls). The guidance document entitled "Class II Special Controls Guidance Document: Root-Form Endosseous Dental Implants and Endosseous Dental Implant Abutments" will serve as the special control.	21 CFR 872.3630
Hip joint metal/ceramic/polymer semi-constrained cemented or nonporous uncemented prosthesis		
	(a) A hip joint metal/ceramic/polymer semi-constrained cemented or nonporous uncemented prosthesis is a device intended to be implanted to replace a hip joint. This device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. The two-part femoral component consists of a femoral stem made of alloys to be fixed in the intramedullary canal of the femur by impaction with or without use of bone cement. The proximal end of the femoral stem is tapered with a surface that ensures positive locking with the spherical ceramic (aluminum oxide, $A1_20_3$) head of the femoral component. The acetabular component is made of ultra-high molecular weight polyethylene or ultra-high molecular weight polyethylene reinforced with nonporous metal alloys, and used with or without bone cement. (b)*Classification.* Class II.	21 CFR 888.3353
	(a) A hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis is a two-part device intended to be implanted to replace the articulating surfaces of the hip while preserving the femoral head and neck. The device limits translation 888.3410 and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across the joint. This generic type of device includes prostheses that consist of a femoral cap component made of a metal alloy, such as cobalt-chromium-molybdenum, or a ceramic material, that is placed over a surgically prepared femoral head, and an acetabular resurfacing polymer component. Both components are intended for use with bone cement (888.3027).	21 CFR 888.3410

Table 6. United States government regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

Device/Drug	Rule	Reference
	(b) *Classification* . Class III. (c) *Date PMA or notice of completion of a PDP is required* . A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before January 3, 2005, for any hip joint metal/polymer or ceramic/polymer semiconstrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976, or that has, on or before January 3, 2005, been found to be substantially equivalent to a hip joint metal/polymer or ceramic/polymer semiconstrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976. Any other hip joint metal/polymer or ceramic/polymer semiconstrained resurfacing cemented prosthesis must have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.	
Injections		
	Sec. 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition. (a) The aluminum content of LVP) drug products used in TPN therapy must not exceed 25 µg/L. WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/L/kg/d accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. (f) Applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to the Food and Drug Administration validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment under 314.60 or 314.96 of this chapter.	21 CFR 201.323
	(a)*Ingredients, preservatives, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed: (1) 0.85 milligrams if determined by assay; (2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or (3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2 of this chapter). (b)*Extraneous protein; cell culture produced vaccines.* Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000. (c)*Antibiotics.* A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines. (d) The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research may approve an exception or alternative to any requirement in this section. Requests for such exceptions or alternatives must be in writing.	21 CFR 610.15
OTC Drugs		
	(a) Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of aluminum hydroxide ingredients for the specified uses: (1)*Topical acne drug products.* (3)*Antidiarrheal drug products* --(i)*Approved as of May 7, 1991* . (8)*Digestive aid drug products* --(i)*Approved as of May 7, 1991.* (iii)*Diaper rash drug products.*	21CFR310.545
	(a) Aluminum-containing active ingredients: (1) Basic aluminum carbonate gel. (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum	21CFR331.11

Table 6. United States government regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

Device/Drug	Rule	Reference
	hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated). (3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid. (4) Aluminum phosphate gel when used as part of an antacid combination product and contributing at least 25 percent of the total acid neutralizing capacity; maximum daily dosage limit is 8 grams	
	Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. (a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients [aluminum hydroxide] for the specified uses: Topical acne drug products and antidiarrheal drugs.	21 CFR 310.545
	The labeling of the product contains the following information for anorectal ingredients identified in 346.10, 346.12, 346.14, 346.16, 346.18, and 346.20, and for combinations of anorectal ingredients identified in 346.22. Unless otherwise specified, the labeling in this subpart is applicable to anorectal drug products for both external and intrarectal use. (H) "Temporarily relieves the symptoms of perianal skin irritation." (iv)*For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5).* "For the temporary relief of itching associated with moist anorectal conditions." *For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5).* "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area."	21 CFR 346.14
	Listing of specific active ingredients (a) Aluminum-containing active ingredients: (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).	
	Permitted combinations of active ingredients. (a)*Combinations of skin protectant active ingredients.* (1) Any two or more of the ingredients identified in 347.10(a), (d), (e), (i), (k), (l), (m), and (r) may be combined provided the combination is labeled according to 347.50(b)(1) and provided each ingredient in the combination is within the concentration specified in 347.10. (2) Any two or more of the ingredients identified in 347.10(a), (d), (e), (g), (h), (i), (k), (l), (m), and (r) may be combined provided the combination is labeled according to 347.50(b)(2) and provided each ingredient in the combination is within the concentration specified in 347.10. (b)*Combination of ingredients to prepare an aluminum acetate solution* . Aluminum sulfate tetradecahydrate may be combined with calcium acetate monohydrate in powder or tablet form to provide a 0.13 to 0.5 percent aluminum acetate solution when the powder or tablet is dissolved in the volume of water specified in "Directions."	21 CRF 347.10
Food Packaging		
	Aluminum hydroxide is among the list of substances that may be a component of cellophane as a food packaging substance.	21 CFR 177.1200
	Aluminum hydroxide is included in the list of fillers of rubber articles intended for repeated use may be safely used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21CFR177.2600

LVP - large volume parenteral; PBP – pharmacy bulk packages; SVP - small volume parenteral; TPN - total parenteral nutrition

Table 7. Organizational findings and government regulations with regard to aluminum and related compounds.[27]

Agency	Findings/regulation	Reference
INTERNATIONAL		
IARC	Group 1: aluminum production carcinogenic to humans	[163]
WHO	Drinking water quality guidelines for aluminum ≤0.1 mg/L in large water treatment facilities ≤0.2 mg/L in small water treatment facilities	[164]
UNITED STATES		
Air		
ACGIH	TLV (8-hour TWA) for aluminum and compounds (as Al) Metal dust - 10 mg/m^3 Pyro powders - 5 mg/m^3 Soluble salts - 2 mg/m^3 Alkyls (NOS) - 2 mg/m^3 TLV (8-hour TWA) for aluminum Oxide[a] - 10 mg/m^3	[165]
NIOSH	REL (10-hour TWA) Aluminum 10 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction) Aluminum oxide 15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	[20]
OSHA	PEL (8-hour TWA) for general industry for aluminum metal (as Al) and aluminum oxide 15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	29 CFR 1910.10000
Water		
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act for aluminum sulfate	40 CFR 116.4
EPA	Drinking water standards and health advisories - 0.05–0.2 mg/L	[166]
EPA	National primary drinking water Standards - No data	[167]
EPA	National secondary drinking water standards for aluminum - 0.05–0.2 mg/	40 CFR 143.3
EPA	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act for aluminum sulfate - 5,000 pounds	40 CFR 117.3
EPA	Water quality criteria for human health for aluminum Freshwater CMC - 750 µg/L Freshwater CCC - 87 µg/L	[168]
Food		
FDA	Bottled drinking water for aluminum - 0.2 mg/L	21 CFR 165.110
Other		
EPA	Pesticide exemptions from the requirement of a tolerance Aluminum hydroxide (for use as a diluent and carrier)[c] Aluminum oxide (for use as a diluent)[g]	40 CFR 180.910

[a] TWA: the value is for particulate matter containing no asbestos and <1% crystalline silica.

[b] AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

[c] Pesticide exemptions from the requirement of a tolerance: residues of the following materials are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; Al = aluminum; CCC = Criterion Continuous Concentration; CMC = Criteria Maximum Concentration; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NOS = not otherwise specified; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

Table 8. Clinical trials of medical devices containing alumina.

Study	Results	Reference
Artificial Hips		
Alumina-on-alumina (n = 88 subjects; 107 hips) and alumina ceramic bearing (n = 65; 71 hips) followed for an average of 6.84±1.49 years and 7.73±1.60 years.	No adverse effects from exposure to alumina.	[169]
Two alumina hips compared, with and without alumina grit blasted finish (n = 14, 18) followed for 12 months and compared for complications.	Alumina particles on the surface of prostheses has a histologically observable impact on surrounding tissues and leads to surface wear in vivo, This was considered mechanical and not a reaction to alumina.	[170]
Alumina-on alumina (n = 849; 930 hips) followed for an average of 5.9 years for adverse events, 10 years for survivorship.	All adverse event/complications were of mechanical origin, not from exposure to alumina. Survival[1] of the hips at 10 years was 96.8%.	[171]
Fine-grained alumina ceramic hips, with and without zirconium oxide added (n = 29 women, 35 men and 21 women, 24 men) followed for an average of 73 (26-108) and 72 (31-98) months.	Survivorship was 95% and 93% at 6 years, respectively. There were no cases of osteolysis in the first group and 1 case in the second. No adverse effects attributed to alumina were reported.	[25]
Alumina-on-alumina hips (n = 77, 82 hips) were retroactively followed for 8 years.	8 year survival was 90.7% with no revisions, 94.4% with revisions. All issues were attributed to mechanical issues and not from exposure to alumina.	[172]
Alumina ceramic hips (n = 301) were followed for at least 10 years.	Survival was 98% (confidence interval 94.2%-99.6%) at 10 years. All adverse effects were due to mechanical issues.	[173]
Two alumina ceramic hips compared (n=27, 23) comparing an alumina and a polyethylene liner followed for 2 years.	No adverse effects from either form of hip.	[174]
Dental Implants		
Alumina ceramic attachment (> 95% alumina) to hold dentures (n = 20) were followed for 1 year.	No adverse effects from exposure to alumina.	[175]
Single crystal alumina endosteal dental implants (n = 29) followed for 5 years.	5 implants removed from study due to mechanical issues, infection, or patient discomfort. No adverse effects from exposure to alumina.	[176]
Single crystal alumina endosteal dental implants (n = 23; 15 subjects) followed for 10 years. 6 weeks after implantation, the implants served as abutments for fixed prostheses.	After 10 years 2l baseline implants were still in place, I7 were fully functional (81% survival). All adverse events were mechanical and not due to exposure to alumina.	[177]
Glass infiltrated alumina crowns (n = 5a; 21 subjects) followed for 5 years.	All adverse events were mechanical and not related to exposure to alumina.	[178]
Other Devices		
Retrospective study (n = 12) of internal alumina/ceramic composite stents inserted for treatment of traceomalacia were followed.	None of the complications were due to the materials. In an assessment of biocompatibility, the authors concluded that there were no foreign body reactions, the inserts were stable, and were a long-term solution with proper suturing technique	[26]

[1] Survival refers to how long the prosthesis is functional.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

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

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

DATE: July 17, 2013

SUBJECT: Comments on the Tentative Report on Alumina and Aluminum Hydroxide

Key Issues

As Alumina and Aluminum Hydroxide contain aluminum, it does not make sense to state in the Abstract that "This safety assessment does not cover aluminum." The report now includes an "overview of aluminum toxicity". It would be more appropriate for the Introduction to include a discussion as to why this report is not an extensive review of aluminum, e.g., "Because, systemic exposure to aluminum from cosmetic use of Alumina and Aluminum Hydroxide is expected to be minimal, this report is not a comprehensive review of the safety of aluminum."

p.8 – The last sentence of the Alzheimer's Disease section is misleading and still suggests that aluminum may have a role in the development of this disease. The Alzheimer's Association says: "During the 1960s and 1970s, aluminum emerged as a possible suspect in causing Alzheimer's disease. This suspicion led to concerns about everyday exposure to aluminum through sources such as cooking pots, foil, beverage cans, antacids and antiperspirants. Since then, studies have failed to confirm any role for aluminum in causing Alzheimer's. Almost all scientists today focus on other areas of research, and few experts believe that everyday sources of aluminum pose any threat." This statement is found at http://www.alz.org/alzheimers_disease_causes_risk_factors.asp .

p.8 – There is too much emphasis on the Dabre study in the Breast Cancer subsection. This section should also discuss the lack epidemiological evidence of the association between antiperspirant use and breast cancer, such as the 2002 study by Mirick (J Natl Cancer Inst 94(20): 1578-1580, 2002) (abstract attached). Also see the National Cancer Institute (NCI) statement on antiperspirants and breast cancer found at http://www.cancer.gov/cancertopics/factsheet/Risk/AP-Deo . NCI states: "There is no conclusive research linking the use of underarm antiperspirants or deodorants and the subsequent development of breast cancer."

p.9 – The last sentence of the Summary is misleading and should be deleted. Where are the studies that looked at the association between Alumina and Aluminum Hydroxide as used

in cosmetics and adverse effects? High exposure to aluminum, such as might occur in dialysis patients taking aluminum antacids has been associated with some effects (osteomalacia, dialysis encephalopathy). Use of Alumina and Aluminum Hydroxide would not result in significant exposure to aluminum. Although there are reports of associations between aluminum exposure and Alzheimer's disease, the predominant scientific opinion is that every day exposure to aluminum does not contribute to this condition.

p.9 – In the Discussion it is misleading to state that: "The concerns about connections of aluminum with Alzheimer's disease and breast cancer are not relevant to the ingredients in this report." is misleading. There is not only no connection to the ingredients in this report, most scientists would conclude that there is no association between these conditions and aluminum exposure.

Additional Comments

p.3 – When discussing data submitted to FDA to support the safety of OTC drugs and medical devices made from Alumina and Aluminum Hydroxide, the phrase "minimizes the need to duplicate that data" does not seem appropriate. This appears to be saying that studies will be repeated when it probably should state "minimizes the need to re-summarize the data".

p.5 – The occupational exposure limits and other exposure limits do not belong in the Use section.

p.5 – The Color Additives section should not be a subsection under "Alumina in Medical Devices".

p.5 – What oral doses of Aluminum Hydroxide were used in the studies in rats in which levels of aluminum were increased by concurrent administration with citric, lactic, malic, oxalic and tartaric acids (references 28-30).

p.6 – It is not clear which groups the 18.0 ± 10.2 ppm and 11.0 ± 4.80 ppm represent.

p.7 – Please correct: "Overview of Amuminum Toxicity"

p.7 – The overview needs to make it clear that the two ingredients reviewed in this report are not considered antiperspirant active ingredients by the US FDA.

p.8 – The beginning of the Breast Cancer section states incorrectly that Aluminum Hydroxide is an active ingredient used in antiperspirant products. At least in the United States Aluminum Hydroxide is not an approved active in OTC antiperspirant products.

p.8 – In a number of places in the Breast Cancer section, the spelling of "chlorhydrate" needs to be corrected.

p.9 – In the Summary, please identify the OTC drug products for which Aluminum Hydroxide is a US FDA approved active.

p.9 – Please correct: "increase is skeletal abnormalities"

p.9 – Rather than stating exposure to aluminum from using cosmetics containing Alumina and Aluminum Hydroxide are "well below the levels of toxicological concern" it would be helpful to state that the levels are well below aluminum levels found in the diet.

p.13-14, Table 6 – The title of the table should indicate that these are United States regulations. It is not necessary to repeat the information in the CFR word for word. 21 CFR 872.3630 appears to have nothing to do with Alumina or Aluminum Hydroxide. Please delete: "(See 872.1(e) for the availability of this guidance document)". Under Injections, please delete "Address in Discussion". Please identify the type of OTC drug actives to which the CFR citations refer.

p.15-16, Table 7 – This Table is not necessary for CIR reports. A similar table can be found in the ATSDR profile on aluminum. Why publish a table that is already available elsewhere? If the table remains in the report, the following corrections should be completed. Explain what is meant by "National" (this report will eventually be published in the International Journal of Toxicology, so the meaning of "National" may vary depending on where you live. All of the information on aluminum phosphide should be removed from the table as it is not relevant to Alumina or Aluminum Oxide.