Safety Assessment of Alumina and Aluminum Hydroxide as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: November 15, 2013
Panel Meeting Date: December 9-10, 2013

November 15, 2013

MEMORANDUM

To: CIR Expert Panel and Liaisons

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Senior Toxicologist

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

In September, the Panel reviewed the Draft Final Report of alumina and aluminum hydroxide. At the request of the Personal Care Products Council, this report was tabled to incorporate suggested edits. There were no public comments and no new data were submitted. The comments from industry were addressed.

The discussion of the current state of research of aluminum and perceived connections to osteomalacia, dialysis encephalopathy, breast cancer, as well as Alzheimer's disease has been moved to an appendix.

The Panel should review the Draft Final Report and ensure that the Abstract, Discussion, and Conclusion reflect the Panel’s thinking. The Panel should then issue a Final Report.
# SAFETY ASSESSMENT FLOW CHART

## Public Comment
- 60 day public comment period

## CIR
- Draft Priority List
- Draft Priority List
- Priority List

## Expert Panel
- Priority List
- Decision not to reopen the report

## Re-Reviews
- Is new data cause to reopen?
- Does new data support adding new ingredient?
- 15 years or New Data; or request

## Report Color
- Buff Cover
- Green Cover
- Pink Cover
- Blue Cover

### Chart Details
- **Announce**
- **Public Comment**
- **CIR**
- **Expert Panel**
- **Re-Reviews**
- **Report Color**
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 examined the Draft Final Report and ensures that the Abstract, Discussion, and Conclusion reflect the Panel’s thinking. The Panel reviewed the new section on aluminum toxicity to ensure that it covers the issues that the Panel considers necessary. The Panel tabled the report to allow for time to address Council comments.

December, 2013 – The Panel examined the Draft Final Report and ensures that the Abstract, Discussion, and Conclusion reflect the Panel’s thinking. A Final Report should be issued.
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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 pharmaceuticals.

Mined “TOXICOLOGICAL PROFILE FOR ALUMINUM” by Health and Human Services for data on aluminum hydroxide.
Transcripts for Alumina and Aluminum Hydroxide
September, 2013

Dr. Belsito's Team

DR. BELSITO: Okay. So alumina, the June meeting we said they were alumina, aluminum hydroxide insoluble not likely to cross the skin, didn't need sensitization, ingestion from lipsticks possible but the amount not a toxicologic concern. Need to point out that the cosmetic ingredient was not aluminum but make a little statement that we're aware of concerns regarding aluminum and Alzheimer's disease as well as some other tox endpoints which I think the writer did a good job on.

And so, we're here to decide whether that's it. It looks like I had some typos. I don't know if anything is really substantive. Okay in the abstract, the next to the last sentence it says, the safety assessment does not address aluminum as a cosmetic ingredient. Do we want to say that?

MR. ANSELL: Well, we have a real problem with the amount of aluminum included throughout the entire report. We open with this is about alumina hydroxide not aluminum and yet we have massive sections in the toxicology about aluminum. We have the DARPA papers brought up about breast cancer and aluminum. We got aluminum reports and its use in drug applications. We have its use in antiperspirants. Its use in --

DR. BELSITO: But that's aluminum chloride and aluminum hydroxide which we're looking at.

MR. ANSELL: It's --

DR. BELSITO: The breast cancer is aluminum but we said we wanted to put a little bit in the Alzheimer's but we said we wanted to put a little bit in there to show that we're aware of it.

MR. ANSELL: Right, and we think that --

DR. BELSITO: You think there's too much?

MR. ANSELL: Way too much.

MR. BOYER: Well, there's a whole section now on aluminum toxicology and that's towards the end of the document.

DR. BELSITO: Right.

MR. BOYER: And I think that the Panel at the last meeting requested that kind of a write-up to begin with.

DR. BELSITO: We did.

MR. BOYER: And that's, I mean, that's why that's in there at the present time. But I believe the Panel's intention was to determine whether or not first of all that met the need, second to what extent it might be reduced and where it might be placed as well. And I think one of the Council's comments was that a lot of this could be condensed or that particular section could be condensed and incorporated into the introductory section. And dealt with right up front.

DR. BRESLAWEC: We don't have any issues with discussing the toxicity information but it has to be placed in context and the relevance of the data that are presented here. It needs to be identified, highlighted. The Panel is well aware of the differences between the different ingredients. The Panel is well aware of the nuances but somebody reading this report who's not aware of it, really it's very difficult to follow in that sense. This is a very important ingredient for the cosmetic industry and there are issues surrounding similar sounding ingredients.

So the report has to be tight. It has to be robust and it has to be credible because the industry and the others will be using this report.
So our request is to table the report so that we, at least, have another chance to take a look at how it's rewritten so that the relevance of the various toxicity sections which are well written and we don't have a problem including them, but so the relevance of those toxicity sections on the ingredients that they're tested is clear, vis-à-vis the ingredients that are under review. We don't think the current report clearly does that. There are a lot of phrases throughout the report that when taken out of context, just taken even in context don't make a lot of sense.

DR. LIEBLER: So, you know, as I read this and I hear this discussion I think that this might be an example of something that we might be able to address effectively with some of the improvements in electronic publishing. And a lot of papers that we write now, we have a section of data or something like this where it needs to be mentioned and there's a lot that we've done that we've put in supplemenal data. See supplemental results. See supplemental discussion, see supplemental this or that and then the journal will have that supplemental stuff. It's just a hyperlink away for the reader.

But this could be dealt with in the introduction that this report is on alumina which it's chemically defined as such and such and not on aluminum or aluminum compounds which nevertheless have attracted tremendous interest because of other toxicities and health concerns. The panel considered this literature and see supplemental discussion. And it could be dealt very effectively with that if the journal uses that format or presentation and that way and we could use this is a way to streamline our reports in certain cases by parking the relevant stuff out of the logic flow of our main document but still making it clear that the Panel actually reviewed the literature and considered it and was able to explain why it's distinct from the ingredients that are being reviewed in this particular report.

And if we did that and also combed through for what you're concerned about which would be inappropriate mentions, you know, little small editorial things, I think it's problem solved. And the only question I have is will the International Journal of Toxicology, does it utilize supplemental information?

MS. GILL: I don't know if it does or not.

DR. SNYDER: I think we've broached that one time before about having supplemental and they currently don't.

DR. LIEBLER: And we should check because that's something that is, if they do we should check because that's the way to do this, the 21st century.

DR. BELSITO: Well, I guess the question is this was a final report. You're not asking us to change our conclusion. You're simply, what you're suggesting is that there be editorial changes made to the body of the document not to the conclusion, is that correct? You don't want us to say these are unsafe?

DR. BRESLAWE: No, absolutely not.

DR. BELSITO: Right, and we've already said they're safe.

DR. BRESLAWE: But I think we would like an opportunity for review. I mean it has statements in there saying alumina and aluminum hydroxide as used in cosmetics are not approved active ingredients in antiperspirant products. Well, neither has it killed yet. I mean --

DR. BELSITO: But I guess my point is do we need to table this or can we just finalize it and allow you to make cosmetic changes before it goes to print?

DR. BRESLAWE: This is a really important ingredient for the industry. It has to be a cohesive report that we can use and it's a report that's written in sections that isn't tied together. And that's where my concern is.

DR. BELSITO: I understand. But does that require that we table this or can we not say our final conclusion these are safe as used and then let you people do whatever editorial tightening up you want to do?

DR. BRESLAWE: Well, if you say safe as used and don't table it, we don't get an opportunity to comment on it.
DR. BELSITO: Well, that's what I'm asking.

DR. BRESLAWEC: Now, we would like an opportunity to comment.

DR. BELSITO: That would be the case. But you had days, 60 days.

DR. BRESLAWEC: And we made comments and these are comments on the report that has incorporated our comments.

MS. GILL: I think this is -- some of the comments we got quite late. I think we got those Thursday, Wednesday or Thursday about tabling the report. So the report as written doesn't incorporate that request to tighten it up and to make sure that the use of aluminum and where it's confusing isn't there. So.

DR. BELSITO: If our regulations require that if we go final you don't the opportunity to make your editorial changes then I don't have a problem with tabling it. I was just asking the question couldn't we go final and let you make your editorial changes? And what I'm hearing is no. Once we finalize it that this has been encrypted and chiseled in stone and no changes can be made. Fine, table it. Are we all okay with that?

DR. LIEBLER: Yes, International Journal of Toxicology does include supplemental information.

MS. GILL: It does?

DR. LIEBLER: I just looked on their current online table of contents, yes. There's an article with supplemental information as a separate hyperlink. So it's a vehicle that you can use to do reports.

DR. BELSITO: Okay.

MS. GILL: But I'm not sure in this case it would address the council. So I think you can --

MR. ANSELL: The movement to respond to the Panel's desire would be satisfied by moving it into supplemental information. And I think the suggested text that we understand that there's confusion between aluminum, aluminum salts, aluminum hydroxide in the text and then referring people to if you're interested in aluminum, here's where to look, would be entirely consistent.

MS. GILL: So, Jay, would it need to be tabled if that section were supplemental information and then the words Dan suggested at the beginning. Some language in the introduction about that information as found there and so did the use and the terminology, the corrections made about what's a --

MR. ANSELL: I think the amount of editorial work within the body really we want another shot to look at it. And if that requires tabling within the process then yes we would want to table it. And then idea that you can move all the data that's been pulled out into supplemental is fine but it's really the report as stands that we want to have a --

DR. BELSITO: We table it.

Dr. Marks’ Team

DR. MARKS: Next is alumina. And we're also looking at these ingredients, alumina and aluminum hydroxide, at the stage now to issue a final safety assessment.

In June, we had issued a tentative conclusion of "safe," so I think we can move on with a final assessment, with a conclusion of "safe."

But there was a section on aluminum toxicity added to the report, and so I'd ask Ron, Ron, and Tom -- that's page 30 of this -- if there are any significant editorial changes. And then the other is, do you like the section, and is it relevant?

DR. SLAGA: I liked the overview. It was a nice summary. And I didn't have any substantial changes.
DR. MARKS: Rons?

DR. SHANK: I think it's fine.

DR. HILL: I thought it was great. I liked that section.

DR. MARKS: Okay.

DR. HILL: I had a small question about the -- but I think it's just -- it was on the teratogenous -- yes, I think, yes repro and developmental, its teratogenicity, its teratogenicity. There was a statement in there that said aluminum was not detected in whole fetuses, which is impossible, because we have (inaudible) aluminum in our bodies. So I wanted to make sure that I left a comment there, that we were talking about did we not see -- did they use radioactivity, and they didn't see it transferred to the fetuses? Or they didn't see an increase? That was the only question I had.

But the statement as its written makes no sense, because we've got plenty of aluminum in our bodies.

DR. MARKS: Halyna.

DR. BRESLAWEC: Yes -- we liked the toxicity section, as well. The Panel had requested it, and we think that a robust discussion of aluminum toxicity is necessary.

Our concern is that there is no discussion of the relevance of the data summarized in the toxicity section to the ingredients that are being reviewed here for safe use in cosmetics. And we would like to see that discussion developed and put in the report, and that the report be tabled so that the Panel can get a chance to look at the discussion.

Our concern is alumina is a very important ingredient in cosmetics. There are challenges to safe use of alumina. And we, in the industry, we would like to be able to use this report with confidence in the defense of alumina as an ingredient. And, as the report stands, the relevance is missing. And we believe that the discussion in the toxicity section lacks context vis-a-vis what we're reviewing here.

DR. HILL: So, I didn't see it that way, because I thought if you read it in the context of what -- the information that was beautifully done in the toxicokinetic section earlier, about the complete lack of absorption, and why you do sometimes see a little bit of absorption with antacid consumption, for example, I thought if you viewed that section in relationship to the toxicokinetic section, there's no such quandary. But I also understand where you're coming from.

So, maybe if it's just done in such to make sure that it ties back. Because, again, what I said repeatedly the last time applies, is in any conceivable cosmetic use and exposure, you're not getting any aluminum in any form that would have an deleterious health consequences. And that's, to me, that message came loud and clear, but --

DR. BRESLAWEC: Right. I completely agree. As an example, in the overview of aluminum toxicity, the very first, the absorption, probably belongs in the toxicokinetic section. The second, the osteomalacia discussion, what is the relevance of that toxicity to use in cosmetics? Not clear, unless, you know, you've really gotten into the area.

And the dialysis encephalopathy, what's the relevance there? That's IV and oral use.

Again, no objection to leaving that in --

DR. HILL: Just make sure that it's loud and clear what the relevance is.

DR. BRESLAWEC: -- but let's -- I mean, the discussion is supposed to be a discussion of it. And the other thing is, you know, the breast cancer, the alumina, aluminum hydroxide as used in cosmetics as active ingredients in antiperspirant products. Well, neither are a bunch of other things.

DR. BERGFELD: Are you suggesting that go in the discussion, that clarification?

DR. BRESLAWEC: We would like to see this document one more time before it goes, and that the data
that are appropriately presented here, on toxicity, are presented in a more contextual, relevant discussion. And we'd like to take a look at it one more time.

DR. BOYER: And one of the suggestions that industry had, that I thought was (inaudible) a lot of that aluminum toxicity discussion into the introduction.

And we could easily pare it down, make it more brief and more concise, and so forth, and provide a context within an Introduction section. And I think that will more or less take it away from the subsequent discussions of alumina and aluminum hydroxide, the actual ingredients that we're looking at.

And the other point that industry made is that, in fact, there is a consensus out there that there is no causal link between aluminum exposure and Alzheimer's disease, and so forth. We more or less hedged on that, and we can also make it much more clear that, in fact, there is a consensus on that.

DR. HILL: I think you should hedge on that. There's some new -- I've been pretty deep into the Alzheimer's literature for the last couple of years, and I think the things that can be said is, there's some new and pretty suggestive information that there may be some epigenetic-related effects, and that science wasn't there heretofore to even look at.

I think when you get into using epidemiology, what that belies is that it's not just one disease, there's at least two major flavors of it. But even you get down into the disease itself, there are -- the genome-wide association studies keep spitting out new genes of relevance. And what that says is that a combination of a particular person's genetics and their environment comes into play in such a way that if you lump all those people together, and try to look for associations, you will automatically wash it out.

So I'm not saying there is anything that definitely suggests there is a relationship. And, again, it's totally not relevant to cosmetic use of alumina, but I don't think you can completely discount it. You have said, I think, there's consensus. I think you said it pretty loud and clear. From where I sat, it was just right, in terms of, I think, the science that's known.

And I know where Halyna's coming from, but --

DR. BRESLAWEC: No, I was wondering if you had any citations, or any studies, that you can present to the Panel for consideration on the subject.

DR. HILL: I didn't bring that reference, and anybody that referenced it. But it's pretty recent. And again --

DR. BRESLAWEC: Could you provide that? Well --

DR. HILL: Yes, I can. I'll have to do the search again tonight, because I didn't write it down. But I think -- so, the point is, to completely write it off, because there is new science, based on epidemiology studies would be wrong, because we're lumping together -- it's like when you do clinical studies, if you -- for cancer chemotherapeutic, if you put together people who genetically are unable to respond, then you're going to wash out the response. And it's similar in this case.

And I don't think -- again, the point is, from any cosmetic use, by any conceivable route of exposure, you're not getting any aluminum into the system in any form that could do anything, including these epigenetic relationships.

You'd have to have a lot of systemic aluminum. And I don't think -- that's the point. And maybe we make the point even more loud and more clear that, by cosmetic use of these ingredients, you're not going to increase the amount of aluminum in anybody's body, and that's it. Problem solved. All is well.

DR. MARKS: So, Halyna, that last paragraph in the introduction, on page 25, I thought was very clear. It begins with "Note," and then it points, I think, what you want to express very clearly, why that section's in there, and that there is not-it also talks about the extensive research has failed to support associations with Alzheimer's, breast cancer, or other health issues.

So I don't know if you want that restated in the aluminum toxicity section. But, to me, when I read it, it looked pretty clear why that was in, and that last paragraph, I thought summarized it really well.

And I guess the editorial comments --

I'd ask Rachel about this, but if they're just editorial, rather than tabling it, could they not be sent out, and then we could approve it by e-mail? But I don't know if that's proper. I'm not sure we need to delay it just to see a couple of editorial comments, because we're all on the same page. We're not worried about aluminum toxicity
with these two ingredients.

DR. BRESLAWEC: The industry would really like a credible, robust report on this, that is clear, and does not further confuse the issue. There are a number of statements in this document -- that are really tough to deal with: "...both amorphic and crystalline alumina data on which forms are used in cosmetics were not available." Okay?

"This safety assessment does not address aluminum as a cosmetic ingredient..." -- that's true, but then there's a lot of discussion on that.
"FDA requires warning on injections that contain aluminum..." -- in the "Discussion."
I mean, it's just there are a lot of loose --

DR. MARKS: Sure.

DR. BERGFELD: Ends.

DR. BRESLAWEC: -- ends. Thank you. You know, it's got to be cohesive, it's got to be a cohesive argument.
And especially for something that this confusing, that we really need solid toxicity and summary that needs to be presented. But it's got to be relevant, it's got to be linked up, to somebody who is not as familiar with aluminum salts toxicity as this particular group is.

DR. MARKS: So, Tom and Rons, do you like the idea of tabling, see industry suggestions? Obviously, Halyna, you'll be writing Lillian as to "these are suggested changes," and then Lillian and Lillian -- Lillian-squared -- and then we can see the next edition, with the editorial changes.
Do you want to table it, as suggested?

DR. SHANK: Is it necessary to table it? Aren't these editorial changes?

DR. MARKS: That's sort of what I --

DR. SLAGA: I think it's editorial. I --

DR. HILL: So, I would like to see it tabled, just because, depending on how those editorial changes are made -- well, there's editorial and then there's substantive editorial. I'm sure if we get something that industry is comfortable with, it will still be fine with me. But I'd like to see that.
And I just wonder if there's any real downside to table it?

DR. MARKS: I don't see any downside. Rachel, your input, how would you, from a consumer's point of view --

MS. WEINTRAUB: Yes, well, first I want to say I thought that the addition of the section greatly improved this report. I thought it was in context. And I thought having this note up front really explained the difference between alumina and aluminum.
But if there is a desire to further clarify, I think we should all see what industry's comments are.
The question for me is, is it possible to do that in a context that's not tabled? Or is the only way to do that back and forth is if it's tabled?

DR. MARKS: I guess it would be if industry could give us the editorial changes tomorrow?

DR. GILL: Yes, I think I'd like to ask industry. Because what I hear is the addition of -- granted, the removal of some things that you've said are incorrect. And I think that's editorial. And I hear one or two clarification sentences, and making sure that there's no tie to these ingredients to aluminum.
Is there specific language that we could propose by tomorrow to add to this paper, to this report, that would allow it to move forward?

DR. BRESLAWEC: When we talked about it with the staff last week, there were pretty substantive changes
that we would propose -- and, really, a discussion of, you know, more of the context. I think Ivan understands what our concern is. I'm not sure we can come up with it tomorrow, by tomorrow. That's a question.

I mean, we certainly will provide comments in whatever format, whether you table it or not. This is an important ingredient. We would like to have an opportunity to review it, and have the panel review it before it goes final.

DR. MARKS: So, what I'm going to propose tomorrow is that it actually -- since you used the word "substantive," I'm going to propose that we table it and see those substantive editorial changes. And then we'll just look at it again in the next meeting.

Is that okay, Ron? I know Ron Hill's -- Ron Shank, and Tom, is that okay?

DR. SHANK: Yes.

DR. MARKS: Okay. Thank you, Halyna. So, tomorrow I'll propose, I'll make a motion we table for industry input on editorial changes. Okay. We'll still have a "safe" conclusion. There's no question about that. But we will see these editorial changes. Okay. Thank you, Halyna.

**Day Two**

DR. MARKS: In June of this year, the Panel looked at the assessment of alumina and aluminum hydroxide and issued a tentative report with "safe" as the conclusion. We're at the stage of the final safety assessment. In our team discussion, industry had a number of editorial inputs which they thought were significant. And so, we felt we should table the issuing of the final safety report with a "safe" conclusion until we see industry's edits.

DR. BELSITO: Second.

DR. BERGFELD: Second. There is no discussion on the table. So all those in favor to table, please indicate by raising your hand.

Unanimous. So we'll be moving on. Is there any comment that you want to make specifically to that table, other than the industry will supply some information?

DR. MARKS: No, unless Halyna wants to make any comments.

DR. BRESLAWEC: I'm not sure that additional information is necessary; rather, a rewrite of the document that places the toxicological information in context.

DR. BERGFELD: Thank you. So a clarification of that.
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 evaluated the safe use of alumina in several medical devices, and aluminum hydroxide in over-the-counter drugs, which included a review of human and animal safety data. The Cosmetic Ingredient Review Expert Panel considered the FDA evaluations as part of the basis for determining the safety of these ingredients as used in cosmetics. Alumina used in cosmetics is essentially the same as that used in medical devices. This safety assessment does not include metallic or elemental 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 report addresses 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 use in medical devices and over-the-counter (OTC) drugs. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded that the cosmetic ingredient alumina is chemically equivalent to the alumina used as part of color additives in medical devices such as bone cements and sutures. Alumina is also a material used in the construction of dental and hip implants. The FDA found that the information submitted for the approval of medical devices containing alumina was adequate, and determined that alumina is safe for use in devices that come in contact with soft tissue, bone, and internal organs. Additionally, alumina is approved by the FDA as an indirect food additive. The Panel concluded that the FDA’s evaluations of alumina in medical devices, coupled with the Panel’s review of information on aluminum hydroxide, were sufficient to support the safety assessment of alumina.

The Panel also concluded that the aluminum hydroxide used in cosmetics is chemically equivalent to that used in OTC antacid products. The FDA found that the information submitted for the approval of those drugs was adequate to support safe use. The FDA also determined that aluminum hydroxide is generally regarded as safe (GRAS) as a direct food additive. The Panel concluded that FDA’s evaluations of aluminum hydroxide as a food additive and OTC drug, coupled with the Panel’s review of primary scientific toxicity data, was sufficient to support the safety assessment of this ingredient as used in cosmetics.

CIR has reviewed several cosmetic ingredients that consist of molecules containing aluminum atoms (Table 2). The conclusion was safe as used for all of these ingredients.

The cosmetic ingredients alumina (aluminum oxide) and aluminum hydroxide are stable, oxidized aluminum compounds that differ substantially from aluminum (elemental or metallic) in chemical and physical properties, functions, and potential for toxicity. There has been substantial discussion in the literature about speculations that exposure to elemental aluminum or aluminum compounds could play a role in the etiology of Alzheimer’s disease, breast cancer, and other health problems. Overall, scientific research has failed to find cause and affect relationships. Furthermore, systemic exposure to aluminum from the use of alumina and aluminum hydroxide in cosmetics is expected to be negligible. The Panel considered the toxicological literature on aluminum and was satisfied that much of the speculations about aluminum toxicity are not relevant for the assessment of the safety of alumina and aluminum hydroxide as used in cosmetics. A brief overview of aluminum toxicity is attached, below, to provide supplementary information 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 presented in Figure 1.

Alumina, also known as aluminum oxide (Al₂O₃), 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. Figure 1 schematically depicts both amorphous and crystalline alumina.

Aluminum hydroxide, also known as hydrated alumina, is most commonly found as the polymorphic mineral gibbsite (a component of the aluminum ore known as bauxite).¹² 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. The properties of the starting materials (pH, presence of anions or salt, and mineral surfaces) 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, which 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. Categorization is based on crystallographic structures found under environmental conditions and cited most often in the literature (Table 3). The \( \alpha \) prefix is generally applied to hexagonal close-packed and related structures; these are aluminum minerals abundantly found in nature. The \( \gamma \) 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 \( \alpha \)-phase minerals). The \( \gamma \)-phase has cubic close-packed lattices or other, 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). The presence of trace amounts of chromium or cobalt creates ruby and sapphire, respectively.

Aluminum compounds cannot easily be oxidized, and thus atmospheric oxidations generally are not expected to occur.

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

**Method of Manufacture**

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

**Impurities**

Alumina balls used in artificial hips must meet the following specifications: grain size < 5 microns and purity > 99.7% aluminum oxide. The maximum percentages for trace substances permitted are: MgO, 0.2%; SiO\(_2\), 0.01%; CaO, 0.03%; Na\(_2\)O, 0.02%; Fe\(_2\)O\(_3\), 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\(_2\)O\(_3\)) ≥ 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). A survey of the maximum use concentrations has been conducted by the Personal Care Products Council (Council). 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 at 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. 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. Two other chewable tablets were approved...
with aluminum hydroxide:magnesium trisilicate doses of 80:20 mg and 160:40 mg. Liquid suspensions of aluminum hydroxide are also used as antacids.

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 of age (Table 6) (21 CFR 247.10; 21 CFR 347.50).

Alumina is used as an adsorbent, desiccant, and abrasive. 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.

Alumina is approved as an indirect food additive by the FDA. Aluminum hydroxide is considered GRAS as a direct food ingredient by the FDA[21 CFR 176.210, 177.1200, 177.2600]. 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 ASTM F603-12, “Standard Specification for High-Purity Dense Aluminum Oxide for Medical Application.”

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

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

Color Additives

Colors that contain alumina (e.g., 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). The colors are created by applying the coloring material 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 alumina/ceramic composites have been approved for use on hip joint replacements in humans. The materials conform to FDA's "Guidance document for the preparation of premarket notifications for ceramic ball hip systems." One of these hip replacement products was reported to consist of ~75% alumina, ~25% zirconia, and < 1% chromium oxide.

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. These stents are implanted inside 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. 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 hydroxide precipitates of denatured keratin in the cornified layer that surrounds and occludes the opening of sweat ducts.31 This mechanism suggests 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 [26Al]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 7 and 21 days thereafter. The treatment group had increased aluminum in the tibiae-fibulae, ulnae-radii, leg muscles, and kidneys. At day 21, all aluminum content measurements were similar to controls.

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 (< 0.01%) in humans.35,36 Using 26Al, 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 for the citrate form and least for aluminum hydroxide. The addition of citrate to the aluminum hydroxide increased the 26Al 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 estimated to be 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/d 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 carboxymethyl 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 as
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. However, there were no differences in total 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 altered, and there was an increase in the amount of calcium excreted in the feces. The rate of skeletal Ca++ accretion was decreased without 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. When compared to the control group (n = 3 females, 2 males) urinary Al was ~ 10- to 20-fold greater during treatment. The authors stated 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.

**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. 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. Fetal body weight was reduced and skeletal variations (delayed ossification of occipital bone and sternebrae; absence of xiphoids) were increased in the aluminum hydroxide plus citric acid group. The absence of xiphoids 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 accumulation was not detected in whole fetuses of the treated mice compared with those in the control group (n = 17), which were 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. 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 artificial hips (with alumina-on-alumina ball and socket contact 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. None of the failures were attributed to adverse reactions to the alumina.
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.

The alumina and aluminum hydroxide produced for cosmetics is chemically equivalent to the materials used to color surgical sutures and to the alumina in other medical devices, as well as to the alumina in OTC drugs. The safety information submitted for those medical devices and drugs was reviewed by the FDA, including the results of acute and long-term biocompatibility testing for cytotoxicity, irritation and intracutaneous reactivity, sensitization, systemic toxicity, implantation effects, and hemato compatibility studies. The FDA found the 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. Alumina is approved as an indirect food additive. Aluminum hydroxide is GRAS as a direct food additive and safe for use in OTC drugs.

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 in 6 rinse-off products up to 8.8% (in oral hygiene products).

Alumina is used in color additives for sutures, and is a material in the construction of endosseous dental implant abutments and femoral bearing heads of artificial hips.

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

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

Aluminum hydroxide orally administered to rats at 2400 mg/kg had no effect on cognitive abilities, but 100 mg/kg administered with citric acid reduced the rat’s learning ability.

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

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

Aluminum hydroxide at 10% was not dermally irritating to mice, rabbits, or 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 noted that the scientific literature provides no plausible evidence linking Alzheimer’s disease or breast cancer to the use of these ingredients.

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 could be released in the digestive tract through the incidental ingestion of such cosmetic products are far below levels of toxicological concern.

There was no concern about dermal penetration or cosmetic application around the eye because these ingredients are practically insoluble and are not irritant to the skin or eyes.

The Panel discussed the issue of incidental inhalation exposure to alumina and aluminum hydroxide in cosmetic powders and fragrance preparations. 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 available. 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 and Aluminum Hydroxide Structures](image)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>CAS No.</th>
<th>Definition</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alumina</td>
<td>1333-84-2</td>
<td>Alumina is an inorganic compound that conforms to the formula: Al₂O₃. <em>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.</em></td>
<td>Abrasive, absorbent, anticaking agent, bulking agent, opacifying agent</td>
</tr>
<tr>
<td></td>
<td>1344-28-1</td>
<td>(hydrate ‘hydrate’ in reference to Alumina often means Aluminum Hydroxide or something between Alumina and Aluminum Hydroxide); alternative CAS No. for 21645-51-2</td>
<td></td>
</tr>
<tr>
<td>Aluminum hydroxide</td>
<td>1333-84-2</td>
<td>Aluminum hydroxide is an inorganic compound that conforms to the formula Al(OH)₃ · xH₂O. <em>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.</em></td>
<td>Opacifying agent, skin protectant</td>
</tr>
<tr>
<td></td>
<td>21645-51-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The italicized text below represents additions made by CIR staff.*
Table 2. Cosmetic ingredients containing aluminum that have been reviewed by CIR.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Conclusion</th>
<th>Maximum concentration (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alumina, magnesium metasilicate, aluminum calcium, sodium silicate, sodium potassium, aluminum silicate</td>
<td>Safe as used when formulated to be non-respirable.</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>Aluminum citrate</td>
<td>Safe as used.</td>
<td>80</td>
<td>49</td>
</tr>
<tr>
<td>Aluminum dimyristate, aluminum isostearates/myristates, aluminum myristate, aluminum palmitates</td>
<td>Safe as used.</td>
<td>82</td>
<td>50,51</td>
</tr>
<tr>
<td>Aluminum silicate, magnesium aluminum silicate</td>
<td>Safe as used.</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>Aluminum starch octenylsuccinate</td>
<td>Safe as used with limitations on heavy metal content.</td>
<td>30</td>
<td>53</td>
</tr>
<tr>
<td>Aluminum distearate, aluminum stearate, aluminum tristearate</td>
<td>Safe as used.</td>
<td>25</td>
<td>54,55</td>
</tr>
<tr>
<td>Calcium aluminum borosilicate</td>
<td>Safe as used.</td>
<td>97</td>
<td>56</td>
</tr>
<tr>
<td>Potassium aluminum polyacrylate</td>
<td>Safe as used when formulated to be nonirritating.</td>
<td>25</td>
<td>57</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Mineral Name</th>
<th>Chemical composition</th>
<th>Common crystallographic designation</th>
<th>Past accepted crystallographic designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibbsite (hydrargillite)</td>
<td>Aluminum trihydroxide</td>
<td>α-Al(OH)₃</td>
<td>γ-Al(OH)₃</td>
</tr>
<tr>
<td>Bayerite</td>
<td>Aluminum trihydroxide</td>
<td>β-Al(OH)₃</td>
<td>α-Al(OH)₃</td>
</tr>
<tr>
<td>Nordstrandite</td>
<td>Aluminum trihydroxide</td>
<td>Al(OH)₃</td>
<td>α-Al(OH)₃</td>
</tr>
<tr>
<td>Doyleite</td>
<td>Aluminum trihydroxide</td>
<td>Al(OH)₃</td>
<td>-</td>
</tr>
<tr>
<td>Boehmite</td>
<td>Aluminum oxyhydroxide</td>
<td>γ-AlOOH</td>
<td>γ-AlOOH</td>
</tr>
<tr>
<td>Diaspore</td>
<td>Aluminum oxyhydroxide</td>
<td>α-AlOOH</td>
<td>α-AlOOH</td>
</tr>
<tr>
<td>Corundum (α-alumina)</td>
<td>Aluminum oxide</td>
<td>α-Al₂O₃</td>
<td>α-Al₂O₃</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical form</td>
<td>Solid, crystalline powder</td>
<td>18,58</td>
</tr>
<tr>
<td>Color</td>
<td>White</td>
<td>18</td>
</tr>
<tr>
<td>Odor</td>
<td>None</td>
<td>58</td>
</tr>
<tr>
<td>Gram formula weight g/mol</td>
<td>101.96</td>
<td>18</td>
</tr>
<tr>
<td>Density/specific gravity @ 20°C</td>
<td>4.0</td>
<td>18</td>
</tr>
<tr>
<td>Viscosity kg/(s∙m) @ 20°C</td>
<td>Solid</td>
<td>18</td>
</tr>
<tr>
<td>Vapor pressure mmHg @ 20°C</td>
<td>Negligible</td>
<td>58</td>
</tr>
<tr>
<td>Melting point °C</td>
<td>2980</td>
<td>18</td>
</tr>
<tr>
<td>Boiling point °C</td>
<td>-2000</td>
<td>18</td>
</tr>
<tr>
<td>Water solubility</td>
<td>Insoluble</td>
<td>18</td>
</tr>
</tbody>
</table>

| Physical form                 | Amorphous powder           | 18        |
| Color                         | White                      | 18        |
| Gram formula weight g/mol     | 78.00                      | 18        |
| Density/specific gravity      | 2.42                       | 18        |
| Melting point °C              | 300                        | 18        |
| Water solubility              | Practically insoluble      | 18        |
Table 5. Frequency of use according to duration and exposure of alumina and aluminum hydroxide.

<table>
<thead>
<tr>
<th>Use type</th>
<th>Alumina</th>
<th>Aluminum hydroxide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total/range</strong></td>
<td>563</td>
<td>576</td>
</tr>
<tr>
<td><strong>Maximum Concentration (%)</strong></td>
<td>0.0004-60</td>
<td>0.0000008-10.1</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rinse-off</strong></td>
<td>523</td>
<td>572</td>
</tr>
<tr>
<td><strong>Maximum Concentration (%)</strong></td>
<td>0.0004-60</td>
<td>0.0000008-10.1</td>
</tr>
<tr>
<td><strong>Use</strong></td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td><strong>Maximum Concentration (%)</strong></td>
<td>0.903-25</td>
<td>NS0.0022-8.8</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Exposure type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eye area</strong></td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td><strong>Incidental ingestion</strong></td>
<td>88</td>
<td>155</td>
</tr>
<tr>
<td><strong>Incidental Inhalation</strong></td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td><strong>Incidental Inhalation-powders</strong></td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td><strong>Dermal contact</strong></td>
<td>441</td>
<td>409</td>
</tr>
<tr>
<td><strong>Deodorant (underarm)</strong></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Hair-noncoloring</strong></td>
<td>1</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Hair-coloring</strong></td>
<td>NR</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Nail</strong></td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td><strong>Mucous Membrane</strong></td>
<td>107</td>
<td>157</td>
</tr>
<tr>
<td><strong>Baby</strong></td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

* 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.

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

<table>
<thead>
<tr>
<th>Device/Drug</th>
<th>Rule</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endosseous dental implant abutment</strong></td>
<td>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 &quot;Class II Special Controls Guidance Document: Root-Form Endosseous Dental Implants and Endosseous Dental Implant Abutments&quot; will serve as the special control.</td>
<td>21 CFR 872.3630</td>
</tr>
<tr>
<td><strong>Hip joint metal/ceramic/polymer semi-constrained cemented or nonporous uncemented prosthesis</strong></td>
<td>(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, (A_2O_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.</td>
<td>21 CFR 888.3353</td>
</tr>
<tr>
<td></td>
<td>(b) Classification. Class II.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(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</td>
<td>21 CFR 888.3410</td>
</tr>
<tr>
<td></td>
<td>(d) 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).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(b) Classification. Class III.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(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</td>
<td></td>
</tr>
</tbody>
</table>
Table 6. United States government regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

<table>
<thead>
<tr>
<th>Device/Drug</th>
<th>Rule</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC Drugs</td>
<td>Sec. 350.50 Labeling of antiperspirant drug products. (a) Aluminum-containing active ingredients: (1) Basic aluminum carbonate gel. (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate co-dried gel, aluminum hydroxide-magnesium trisilicate co-dried gel, aluminum-hydroxide sucrose powder hydrated). (3) Dihydroxyaluminum aminocacetate and dihydroxyaluminum aminocetic 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.</td>
<td>21 CFR 350.50</td>
</tr>
<tr>
<td></td>
<td>(e) Warnings. The labeling of the product contains the following statements under the heading &quot;Warnings&quot;: (1) &quot;Do not use on broken skin&quot;. (2) &quot;Stop use if rash or irritation occurs&quot;. (3) &quot;Ask a doctor before use if you have kidney disease&quot;. (4) &quot;For products in an aerosolized dosage form. (i) &quot;When using this product keep away from face and mouth to avoid breathing it&quot;.</td>
<td>21 CFR 310.545</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>21 CFR 310.545</td>
</tr>
<tr>
<td></td>
<td>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) &quot;Temporarily relieves the symptoms of perianal skin irritation.&quot; (iv) For products containing kaolin identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5). &quot;For the temporary relief of itching associated with moist anorectal conditions.&quot; For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5). &quot;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.&quot;</td>
<td>21 CFR 346.14</td>
</tr>
<tr>
<td></td>
<td>Listing of specific active ingredients (a) Aluminum-containing active ingredients: (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate co-dried gel, aluminum hydroxide-magnesium trisilicate co-dried gel, aluminum-hydroxide sucrose powder hydrated).</td>
<td>21 CFR 331.11</td>
</tr>
<tr>
<td></td>
<td>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), (n), 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 &quot;Directions.&quot;</td>
<td>21 CFR 347.10</td>
</tr>
<tr>
<td>Food Packaging</td>
<td>Aluminum hydroxide is among the list of defoaming agents may be safely used in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food.</td>
<td>21 CFR 176.210</td>
</tr>
<tr>
<td></td>
<td>Aluminum hydroxide is among the list of substances that may be a component of cellophane as a food packaging substance.</td>
<td>21 CFR 177.1200</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>21 CFR 177.2600</td>
</tr>
</tbody>
</table>
Table 6. United States government regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

<table>
<thead>
<tr>
<th>Device/Drug</th>
<th>Rule</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect Food Additive</td>
<td>Aluminum hydroxide is among the list of substances that may be safely used as colorants used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, subject to the provisions and definitions set forth in this section. (a) The term colorant means a dye, pigment, or other substance that is used to impart color to or to alter the color of a food-contact material, but that does not migrate to food in amounts that will contribute to that food any color apparent to the naked eye. (b) The colorant must be used in accordance with current good manufacturing practice, including use levels which are not in excess of those reasonably required to accomplish the intended coloring effect. (c) Colorants in this section must conform to the description and specifications indicated. (d) Color additives and their lakes listed for direct use in foods, under the provisions of the color additive regulations in parts 73, 74, 81, and 82 of this chapter, may also be used as colorants for food-contact polymers.</td>
<td>21 CFR 178.3297</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Agency</th>
<th>Findings/regulation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERNATIONAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IARC</td>
<td>Group 1: aluminum production carcinogenic to humans</td>
<td>59</td>
</tr>
<tr>
<td>WHO</td>
<td>Drinking water quality guidelines for aluminum</td>
<td>≤0.1 mg/L in large water treatment facilities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤0.2 mg/L in small water treatment facilities</td>
</tr>
<tr>
<td>UNITED STATES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACGIH</td>
<td>TLV (8-hour TWA) for aluminum and compounds (as Al) Metal dust - 10 mg/m³ Pyro powders - 5 mg/m³ Soluble salts - 2 mg/m³ Alkyls (NOS) - 2 mg/m³ TLV (8-hour TWA) for aluminum Oxide - 10 mg/m³</td>
<td>81</td>
</tr>
<tr>
<td>NIOSH</td>
<td>REL (10-hour TWA) Aluminum 10 mg/m³ (total dust) 5 mg/m³ (respirable fraction) Aluminum oxide 15 mg/m³ (total dust) 5 mg/m³ (respirable fraction)</td>
<td>82</td>
</tr>
<tr>
<td>OSHA</td>
<td>PEL (8-hour TWA) for general industry for aluminum metal (as Al) and aluminum oxide 15 mg/m³ (total dust) 5 mg/m³ (respirable fraction)</td>
<td>29 CFR 1910.10000</td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA</td>
<td>Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act for aluminum sulfate</td>
<td>40 CFR 116.4</td>
</tr>
<tr>
<td>EPA</td>
<td>Drinking water standards and health advisories - 0.05–0.2 mg/L</td>
<td>64</td>
</tr>
<tr>
<td>EPA</td>
<td>National primary drinking water Standards - No data</td>
<td>143.3</td>
</tr>
<tr>
<td>EPA</td>
<td>National secondary drinking water standards for aluminum - 0.05–0.2 mg/L</td>
<td>40 CFR 117.3</td>
</tr>
<tr>
<td>EPA</td>
<td>Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act for aluminum sulfate - 5,000 pounds</td>
<td>40 CFR 117.3</td>
</tr>
<tr>
<td>EPA</td>
<td>Water quality criteria for human health for aluminum Freshwater CMC - 750 µg/L Freshwater CCC - 87 µg/L</td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Clinical trials of medical devices containing alumina.

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Artificial Hips</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alumina-on-alumina (n = 88 subjects; 107 hips) and alumina ceramic bearing (n = 65; 71 hips) followed for an average of 6.8±1.49 years and 7.7±1.60 years.</td>
<td>No adverse effects from exposure to alumina.</td>
<td>66</td>
</tr>
<tr>
<td>Two alumina hips compared, with and without alumina grit blasted finish (n = 14, 18) followed for 12 months and compared for complications.</td>
<td>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.</td>
<td>67</td>
</tr>
<tr>
<td>Alumina-on-alumina (n = 849; 930 hips) followed for an average of 5.9 years for adverse events, 10 years for survivorship.</td>
<td>All adverse event/complications were of mechanical origin, not from exposure to alumina. Survival of the hips at 10 years was 96.8%.</td>
<td>68</td>
</tr>
<tr>
<td>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.</td>
<td>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.</td>
<td>23</td>
</tr>
<tr>
<td>Alumina-on-alumina hips (n = 77, 82 hips) were retroactively followed for 8 years.</td>
<td>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.</td>
<td>69</td>
</tr>
<tr>
<td>Alumina ceramic hips (n = 301) were followed for at least 10 years.</td>
<td>Survival was 98% (confidence interval 94.2%-99.6%) at 10 years. All adverse effects were due to mechanical issues.</td>
<td>70</td>
</tr>
<tr>
<td>Two alumina ceramic hips compared (n=27, 23) comparing an alumina and a polyethylene liner followed for 2 years.</td>
<td>No adverse effects from either form of hip.</td>
<td>71</td>
</tr>
<tr>
<td><strong>Dental Implants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alumina ceramic attachment (&gt; 95% alumina) to hold dentures (n = 20) were followed for 1 year.</td>
<td>No adverse effects from exposure to alumina.</td>
<td>72</td>
</tr>
<tr>
<td>Single crystal alumina endosteal dental implants (n = 29) followed for 5 years.</td>
<td>5 implants removed from study due to mechanical issues, infection, or patient discomfort. No adverse effects from exposure to alumina.</td>
<td>73</td>
</tr>
<tr>
<td>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.</td>
<td>After 10 years 21 baseline implants were still in place, 17 were fully functional (81% survival). All adverse events were mechanical and not due to exposure to alumina.</td>
<td>74</td>
</tr>
<tr>
<td>Glass infiltrated alumina crowns (n = 5a; 21 subjects) followed for 5 years.</td>
<td>All adverse events were mechanical and not related to exposure to alumina.</td>
<td>75</td>
</tr>
<tr>
<td><strong>Other Devices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective study (n = 12) of internal alumina/ceramic composite stents inserted for treatment of tracheomalacia were followed.</td>
<td>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.</td>
<td>26</td>
</tr>
</tbody>
</table>

**Notes:**
- Survival refers to how long the prosthesis is functional.
- TWA: the value is for particulate matter containing no asbestos and <1% crystalline silica.
- Alumina grit blasted finish.
- All adverse effects were mechanical and not related to exposure to alumina.
- The implants were fully functional 81% survival.
- All adverse effects were due to mechanical issues.
- There were no cases of osteolysis in the first group and 1 case in the second. No adverse effects attributed to alumina were reported.
- 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.

**Abbreviations:**
- ACGIH = American Conference of Governmental Industrial Hygienists;
- AEGL = Acute Exposure Guideline Level;
- AI = 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.
OVERVIEW OF ALUMINUM TOXICITY

ABSORPTION

Aluminum in cosmetics and in antiperspirants is not systemically absorbed to any appreciable extent through the skin.\(^{76-78}\) Aluminum is poorly absorbed in both the respiratory tract and the gastrointestinal tract.\(^{79}\)

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%.\(^{35,36,80,89}\) In contrast, the absorption of water soluble aluminum compounds can range from 0.5 to 5%.\(^{79}\) Accordingly, dietary constituents can enhance or inhibit aluminum 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.\(^{77,79,81,96,98-114}\) 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.\(^{79,81,96,115,116}\) 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.\(^{79}\)

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.\(^{117}\) 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.\(^{96,118-122}\) However, others found no increase in aluminum levels in brain tissues of Alzheimer’s disease patients.\(^{96,109,123-126}\) Further, other researchers found patients with elevated brain aluminum levels but with no clinical signs of Alzheimer’s disease.\(^{96,127,128}\) 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.\(^{129}\) 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.\(^{79,130-146}\) 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.\(^{77,79,81,85,96,147,148}\)

Other epidemiological studies have associated total dietary aluminum consumption with increased risk of Alzheimer’s disease.\(^{96,149}\) 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).\(^{81,133,149,150}\) 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).\(^{77,79,96,133,151-156}\) Likewise, no significant association was found between Alzheimer’s disease and inhalation exposure to aluminum dusts and fumes in the workplace.\(^{79,96,157-160}\)

Overall, the available studies have not substantiated a causal link between aluminum exposure and Alzheimer’s disease.\(^{79,81,85,96,161-167}\)

BREAST CANCER

A number of aluminum-containing compounds are used as active ingredients in underarm antiperspirant products.\(^{21 CFR 350.10}\)\(^{99,168-171}\) Compounds approved for this purpose do not include alumina or aluminum hydroxide. However, compounds like aluminum zirconium octachlorohydrate and aluminum chlorohydrate can be used at concentrations up to 20% and 25% by weight, respectively, in the United States and in Europe, and aluminum chloride has been used in antiperspirant products 15% in Europe.\(^{21 CFR 350.10}\)\(^{172,173}\)
Darbre and coworkers have suggested that long-term, regular underarm and breast-area application of products containing potential endocrine disruptors may promote the development of breast cancer. Further, these authors have 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. High concentrations of aluminum salts perturbed estrogen receptor signaling in MCF-7 cells. The results of these experiments indicate that aluminum compounds, particularly water-soluble aluminum compounds at high concentrations, can perturb estrogen receptor-mediated activities in MCF-7 breast cancer cells. However, these observations cannot be considered relevant to the use in cosmetics of alumina and aluminum hydroxide, which are insoluble and are not absorbed through the skin to any significant extent.

Furthermore, there was no association between underarm antiperspirant or deodorant use and breast cancer in a population-based case-controlled epidemiological study conducted in the U.S. Briefly, breast cancer patients (n = 813) were compared with control subjects (n = 793) from the same population, which were frequency matched to the cancer patients by 5-year age groups. Measures of antiperspirant or deodorant use included self-reported regular use (ever), exclusive use of antiperspirant versus deodorant (or vice versa), and regular use within 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.
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