Safety Assessment of Barium Sulfate as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: May 16, 2014
Panel Date: June 9-10, 2014
Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 16, 2014
Subject: Draft Final Report on Barium Sulfate

A tentative report with a conclusion stating that barium sulfate is safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating, was issued at the March 17-18, 2014 Expert Panel meeting. Comments from the Council were received, and have been addressed.

Included in this package for your review is the Draft Final Report on Barium Sulfate, the CIR report history, Literature search strategy, Ingredient Data profile, 2014 FDA VCRP data, Minutes from the March Panel meeting, and comments provided by the Council (pcpe1 pdf file).

It should be noted that study summaries on the skin irritation and sensitization potential of magnesium sulfate in mice, available at the European Chemicals Agency’s (ECHA) website, were added to that safety assessment. The skin irritation study was actually a skin irritation range-finding test that was performed prior to the mouse local lymph node assay. Magnesium sulfate (50%) was classified as a non-irritant. The Panel needs to determine whether these results in any way impact the “safe when formulated to be non-irritating” qualification on barium sulfate that was determined.

Ultimately, after reviewing the available data, the Panel needs to determine whether a final report with the conclusion stated in the first paragraph should be issued at this Panel meeting.
SAFETY ASSESSMENT FLOW CHART

**Public Comment**
- Draft Priority List
- 60 day public comment period

**CIR**
- Draft Priority List
- Priority List INGREDIENT
- SLR
- Announcement
- Decision not to reopen the report
- Draft Report
- ISD Notice
- Draft TR ISD
- Tentative Report
- Draft FR
- PUBLISH

**Expert Panel**
- DRAFT PRIORITY LIST
- IS
- TABLE
- ISSUE TR
- ISSUE FR

**Re-Reviews**
- 15 years or New Data; or request
- Re-review to Panel
- Does new data support addition of new ingredient?
- YES
- NO

**Report Color**
- Buff Cover
- Green Cover (1st time or tabled DR)
- Pink Cover
- Blue Cover

*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.*
CIR History of:

Inorganic Sulfates

A Scientific Literature Review (SLR) was announced on December 2, 2013. Use concentration data received from the Personal Care Products Council (Council) were incorporated prior to announcement of the SLR. Comments from the Council were received during the 60-day comment period.

**Draft Report, Belsito and Marks Teams/Panel: March 17-18, 2013**

The draft has been revised to include sensitization data on ammonium, potassium, and sodium persulfate, which may be useful in evaluating the sensitization potential of all of the inorganic sulfates reviewed in this safety assessment.

The Panel elected to reduce the Inorganic Sulfates report into two separate reports that focus on the highest frequency of use ingredients, namely magnesium sulfate and barium sulfate. Review of the remaining ingredients will be postponed until their frequency of use warrants assessment.

The Panel noted that the history of safe medical use of barium sulfate indicates no significant toxicity concerns for systemic exposures to these ingredients. Furthermore, the extensive clinical experience of the Panel, including the results of numerous patch tests, indicates that barium salts do not have the potential to induce sensitization. The Panel noted that salts of sulfuric acid, such as sodium sulfate, can be irritating to the skin so cosmetic products containing barium sulfate should be formulated to be non-irritating.

The Panel issued a tentative safety assessment for public comment with the conclusion that barium sulfate is safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

**Draft Final Report, Belsito and Marks Teams/Panel: June 9-10, 2014**

Comments from the Council were received, and have been incorporated.
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Barium Sulfate

Literature Searches on Magnesium Sulfate and Inorganic Sulfates
(1/2013 and 12/2013)

PubMed Searches

Search Terms

Barium Sulfate
CAS No. 7727-43-7

Literature Search Updates

4/24/2014
Barium Sulfate

DR. BELSITO: Okay, inorganic sulfates. So the first thing is the persulfates don't belong with the sulfates at all, so they should be moved out. And I think we can go with a safe -- well, no need to reopen because this was the whole purpose for doing this?

DR. EISENMANN: Magnesium sulfate was the lead ingredient. That's the ingredient that should be reviewed.

DR. BELSITO: So the persulfates need to be brought into their own class.

DR. EISENMANN: That's done. That's an old report.

DR. BELSITO: So why were we looking at ammonium and all those other persulfates here?

MR. JOHNSON: Because of the very limited sensitization data on other ingredients. I think copper sulfate was the only ingredient that they --

DR. BELSITO: Yeah, but the persulfates and the sulfates aren't -- you can't do read-across for sensitization for them.

MR. JOHNSON: But that was the reason for including these.

DR. BELSITO: Okay, well, they need to get out of there. If they're not due for re-review, they need to disappear. And then the issue is all of these are driven by toxicities in the metal. Having said that and having read this whole darn thing, it'd be nice to just say safe as used. But then we look stupid grouping them. Yes, Bart?

DR. HELDRETH: All right. So based on the comments that I've heard about this grouping, it seems like people are under the impression that read-across is the only proper rationale for grouping, but it's not. If you remember, we did the 20 natural alpha amino acids. I don't think we used any read-across for phenylalanine over the sodium glutamate. Those ingredients were grouped together because all those alpha amino acids are now a one spot for formulated to go and look and look at the safety of. We were able to contrast the differences between an individual that may have issues with phenylalanine even though there's absolutely no way to read that across to serine or some other fatty acid.

I understand the idea that if we're thinking about read-across that the metal is potentially more of the driver here, but I think it's -- I mean you the Panel are the experts and it's your prerogative to make the call on it -- but I think it's a little bit hard to say that there's great a read-across between copper fluoride and copper sulfate. So even those metals, the driver there, that couterine says something about what that reactivity is going to be there, what the solubility is going to be there.

So if we can look at these as individuals, which was my original intent -- although I would have liked to have spelled it better in our report for you and we can do that in the future if you agree with this -- but look at this as a group of sulfates and contrast the differences there. Maybe you have an issue with barium or maybe you have an issue with the different metals that are within there and that can be described and called out.

DR. LIEBLER: Bart, I think you've made a good point about read-across. I think the read-across rationale breaks down when you leave the organic world.

DR. HELDRETH: I think so.

DR. LIEBLER: And when you're into inorganics, it's a combination of the anion and the cation equivalent substance in these salts, and they both contribute to any pharmacology or any biological effects. So I think that trying to group by metals, we're going to run into the same kind of odd collection of effects, some not totally innocuous and others potentially problematic as we do when we try and group across sulfates.

DR. EISENMANN: But wouldn't it be better to organize the report -- if you're going to put multiple sulfates, to put all of the data together for barium sulfate and all the data on magnesium sulfate rather than by endpoint? If you were going to do multiple ingredients in one report, you should organize the report differently.

DR. LIEBLER: I think you've got a good point, and I suppose you could also consider use and maybe knock out things with really dissimilar uses because the context for how they're included in products can be quite different depending on uses. Most of these have pretty
similar uses, right, most of these sulfates?
  DR. EISENMANN: No.
  DR. LIEBLER: Okay, well, then --
  DR. BRESLAWEC: I have no problem with varied justifications for grouping things together. For example, there's something that was split apart this time around, the hydroquinone and polyhydroxy salt. That was split apart because of chemical dissimilarities and yet the issue that's being evaluated for both of those chemicals, as dissimilar as they may be, is UV bonding or whatever, the UV action on the components. So to me that is an adequate justification.

On this one I think it just stretches too far. You've got a lot of different kinds of uses. You've got a lot of different kinds of chemical properties. And if you look at how you've been doing this with the more organics, you take the base acid and then you add the basic salts. And here sulfuric acid isn't being considered even.
  DR. LIEBLER: Right.
  DR. BELSITO: I'm fine either way. I'm just mad that I spent hours wasting CIR money reading all of this document.
  DR. BRESLAWEC: Again, we would have no problem if the permission here -- you know, you want to split it up and do five or six different ingredients, fine. If you have the justification for doing it because you can't read-across.
  DR. BELSITO: You don't even have common usage for a lot of them.
  DR. BRESLAWEC: Right. You can't.
  DR. EISENMANN: I mean it's clear that putting in the zinc sulfate for zinc and beryllium for aluminum based on the different functions.
  DR. HELDRETH: So what is gained by separating them out into individual reports? If our writers see the same search on each ingredient and it's in the report, whether it's 17 different reports or one report?
  DR. BRESLAWEC: I'll tell you what's gained is you don't have paragraphs and paragraphs that say sensitization data were mixed. Irritation data were mixed. Of course they're mixed because they're different.
  DR. HELDRETH: Okay. So we could have clarification on the contrasts between those different ingredients.
  DR. BRESLAWEC: Well, no, then you characterize the ingredient that you're evaluating.
  DR. EISENMANN: See, I don't know that you need to contrast -- I mean they're different. I mean -- I don't know.
  DR. BRESLAWEC: If your justification for grouping is to provide a contrast, that doesn't seem warranted to me.
  DR. HELDRETH: I didn't say that was the justification.
  DR. BRESLAWEC: No, but that was one of the reasons, that you could contrast the characteristics of the different ingredients and, therefore, figure out what they're like. To me, that's --
  DR. HELDRETH: It's a benefit, it's not a rationale.
  DR. BRESLAWEC: Well, what's the justification?
  DR. HELDRETH: The justification is a formulator that's looking for sulfates to put into their product, we're going to find them in one place.
  DR. EISENMANN: But see I don't think they're looking for a sulfate to put in their product. They're looking for zinc to put in their product, or they're looking for aluminum to put in their product, or they're looking for magnesium to put in their product. They're not looking to put in sulfate. Persulfates yes, they were looking to put persulfates in because those are oxidated, but they're not looking for sulfates to put in their products.
  DR. BRESLAWEC: Magnesium sulfate was the lead ingredient?
  DR. EISENMANN: Magnesium sulfate is the lead ingredient, and I think the other ingredient that has relatively high use is the barium sulfate. So if you did two reports, one on magnesium and one on barium, that would probably be sufficient. I don't think the other ingredients really matter a whole lot. I mean zinc has some, I think. Zinc would be the next, but --
  DR. BRESLAWEC: Copper sulfate has a lot of data in it.
DR. LIEBLER: But uses?
DR. BRESLAWEC: I don't know about the uses. Again from industry point, and I think I'm speaking here on the --
DR. EISENMANN: And you've already reviewed sodium, so that would not need to be reviewed again.
DR. BRESLAWEC: From the industry viewpoint and also I think I speak for the CIR Science and Support Committee, the credibility of CIR reviews and justifications that are being provided with grouping are really important, and we continue to urge you to provide robust justifications.

DR. EISENMANN: Magnesium has 10.
DR. LIEBLER: Oh, sorry. These are flipped. I'm not used to these. Sometimes these tables are presented upside down.
DR. EISENMANN: Wilbur's reports are upside down.

DR. BELSITO: Yeah, Wilbur. You need to follow the format of everyone else. Total uses on top, not on the bottom.
MR. JOHNSON: Sorry. I guess I was thinking in terms of when you add, you add down as opposed to -- and initially there were two different formats. But I'll go with everybody else.
DR. BELSITO: We need to resolve this beta VCR thing, VCR 1.
DR. LIEBLER: Okay, you're right. So it's barium and magnesium that are driving the boat here. Sodium is already reviewed, right?
DR. EISENMANN: Yes.
DR. BELSITO: Okay, so what are we going to do here? We're going to cut this report up and we're going to basically make two reports. We're going to make one on barium and one on magnesium, and then the rest of the metal sulfates are going to be ignored because they're going to be low priority. Is that what we're saying?
DR. LIEBLER: I'm good with that. It's essentially how we dealt with citrus.
DR. BELSITO: Citrus is going to be a bowl of citrus wax.
DR. HELDRETH: So for each of these ingredients, Wilbur's already done the search on these.

DR. BELSITO: Yeah.
DR. HELDRETH: So can't we say that the information is there or it's insufficient?

DR. BELSITO: Magnesium and barium are safe as used. I'm fine. So we're going to split them up. We're going to do magnesium and barium and we're going to ignore the others. And we're going to go as a safe as used conclusion with them.
DR. LIEBLER: What are you saying, Bart? Are you connecting with us?
DR. HELDRETH: I said Wilbur searched all the ingredients that in the report already.

DR. BELSITO: We've got all the information we're going to get, okay. So if we have all that information, is there any information on barium and magnesium that you feel you need to go for a safe as used conclusion?
DR. HELDRETH: And then the other ingredients that are in this report --
DR. BRESLAWEC: Is there adequate information on the other ingredients to say safe as used? I think that's what you're asking. And because you've done the search, can you separately --

DR. BELSITO: I actually think that there is adequate --
DR. EISENMANN: Well, there's no information on silver at all.
DR. BELSITO: Right, and there's no uses.
DR. EISENMANN: Right.
DR. BELSITO: So I would say that --
DR. EISENMANN: And I would think you'd want to do iron a little bit more in
DR. BELSITO: Fine. Let's break them up and look at each by sulfate, but remove all of them except for magnesium and barium from our priority list and deal with them when they come up on the priority list based upon their use. And that will be down the road. Let's not make any decision. Don't delete the information you have, but at this point I think we have more important issues to struggle with through the year than to release all of these documents. Sometimes I think as a Panel that we've gotten pushed a little too hard to try and get numbers out and create these super families. And I think we need to sometimes maybe slow down and say it's not about numbers, it's about safety and it's about important issues. So I'm fine just saying break it down, bring us magnesium and barium sulfate at the next meeting. Don't bring us the other sulfates individually. Don't lose the data you've collected on it. We're going to be looking at priority lists. Why don't we do some back-of-the-napkin calculations as to where these other sulfates will fall in the 2015 priority list based upon their usage? They'll probably fall off that list and things won't change.

DR. HELDRETH: So the direction is for Wilbur to bring back two separate reports?

DR. BELSITO: Yes, one entitled "magnesium sulfate" and the other "barium sulfate." And they will be, as far as I'm concerned, safe as used. So I'm not requesting from industry any data beyond what's already in this report.

DR. SNYDER: He could provide us with new use data on both of those.

DR. BELSITO: Okay. I haven't looked at that. What does it say?

DR. SNYDER: I don't think there's anything substantive there. There's two product categories that have been deleted for magnesium sulfate and there's two additional use in product categories in nail creams and lotions. So there's nothing there that should be of concern.

DR. BELSITO: Right. And then the persulfates will come up whenever their 15 year cycle to come up comes up. Are we done? Any other comments on the sulfates? You're clear on what your mission is, Wilbur? Basically just to draft a discussion for each of those two and safe as used completion.

MR. JOHNSON: Now, one concern. Two new reports will be the result, okay?

DR. BELSITO: Yes.

MR. JOHNSON: So at this particular meeting, is your plan to issue a tentative report with those conclusions?

DR. BELSITO: Yes.

MR. JOHNSON: Okay.

DR. BELSITO: So a tentative report on barium sulfate and a tentative report on magnesium sulfate and that they're safe as used.

MR. JOHNSON: Okay.

DR. BELSITO: And the conclusion won't change. I think we'll have perhaps a discussion and some changes in your discussion section once we see what that looks like. But I don't think we really want to wordsmith the discussion at this meeting at this point given the time and the other documents we need to get through. There's nothing really important in the discussion. I can't remember if there were respiratory uses. We'll handle it with the respiratory boilerplate. If there's not sufficient data on sensitization, I can tell you I've tested with these metals for over 30 years. I don't think I've ever seen a reaction to magnesium or barium, so they're not sensitizers. They're not going to be in the levels of dust that we need to worry about in pneumoconiosis, so all of the tox data that we're seeing on these metal salts just disappears. And if they're irritating, we can say when formulated to be nonirritating. So I mean barium sulfate is an issue. There was one report when it was done with a GI swallow and it ruptured into the perineum or some ridiculous thing like that. Mag sulfate is given as a bowel prep for anyone who's over 50. You'll enjoy it! So let's move on.
Barium Sulfate

DR. MARKS: Right. Increased uses, and that's increase in lipstick, but lipstick category was being used before, so, okay -- safe conclusion. Next is the inorganic sulfates, and Wilbur, you're still -- so this is the first review of this draft. There's 17 inorganic sulfate ingredients, and there -- you included in this the per-sulfates too, which we have previously reviewed, so one of the -- Tom and Ron, are the ingredients okay? The PCPC questions grouping all these ingredients together, particularly the metals -- what needs do you have, so, just the first time -- I expect there will be a significant amount of discussion.

DR. HILL: So if I agree that all of these ingredients should be lumped together when we did the priorities, I was somehow sleeping, given that I'm supposed to have chemistry expertise, that this document even -- I mean Bart's not in here. Oh there he is, I'm sorry -- go away, go out for a minute, because I will be somehow casting indirect aspersion, but, I actually -- if I were grouping these ingredients, I would I have I think six different groupings or seven. I have to count how many colors I used but I object to these all being grouped in this way. I object to lumping a copper ingredient together with sodium ingredient. I object to putting, especially the hydroxylamine -- that ought to get out of this report, because hydroxylamine would drive any toxicity that would come for the most part. So like I say, I actually -- after I looked at these groupings, I stopped reading the rest of the report, because I was so upset by what was lumped here that I had enough. So that -- yes, like I say, if these -- if I agreed to these in whenever we looked at the priorities, I was clearly asleep or I missed that section, or something. But yes -- especially the per-sulfates, but I also -- the ones that are highly soluble, such as sodium potassium sulfate versus ones that would be very insoluble, such as barium -- let's see -- calcium, and then there's some others that the metal should presumably drive any toxicology much more so than the sulfate and that's the way we ought to establish groupings, so to lump in, for example, silver sulfate with these others, to me, makes zero chemical or biochemical sense.

DR. BERGFIELD: Could I ask a question about the groupings? Are you saying that the groupings should be according to their target effect, rather than their chemistry?

DR. HILL: Some sense of what's generally known about the biology of these things -- I think in general we're looking at ingredients that if we were applying to the skin, they're not going anywhere, other than if we have a mucous membrane, perhaps there are some things that would happen locally with those particular things. And I think those would drive any worry about assessment completely. Including inhalation in a few cases, if that comes into play. But I just object to this grouping completely, and I think if we broke it down -- I'm not really sure if you break it into six reports instead of one, which is I think how many colors I've got here, that that would ultimately result in a whole lot more work for the CIR staff, because we would have cleaner reports, plus the same information that's in here could be put into those five or six different reports, and we would be reviewing ingredients that are, I think at the outset, when we started grouping these things, although I wasn't on the panel, the whole idea was no brainer, and this strays far away in my mind, based on my memory of inorganic chemistry, when I studied it, and also, everything I've seen about biology. If iron, silver, calcium, barium -- all of those things -- this is not a no-brainer assemblage.

DR. SLAGA: I agree, too, that the grouping leaves a lot to be desired. I mean, even if you go to function, there's so many different functions, and if you go to metals, there's different types of metals with different activities. But in reading this report -- I finished reading it even though I didn't like the grouping --

DR. HILL: Well, kudos to you.

DR. SLAGA: This has the most mixed results I have ever seen with one grouping. And so just with the exceedingly mixed results, it's hard to come to any conclusion.

DR. HILL: I did skim the rest of the report, honestly -- I didn't stop, but --

DR. MARKS: So what we need -- if you suggested potentially six -- Ron Shank and actually I'll ask Jay, since the Council has also suggested that there's a question grouping these together. I think what we need at this point -- it sounds like we agree that it's not a good idea to group them all together. The question is, how do we want to do it and, four -- I think it was four,
yes, four ingredients in this report have already been reviewed -- the sodium sulfate and the three
per-sulfates, so there's already reports on them. The no-brainer refers to re-opening, Ron Hill.

DR. HILL: Yes.

DR. MARKS: The first time we see it, no-brainer is not applicable.

DR. HILL: I know.

DR. MARKS: So Jay, do you --

DR. ANSELL: Well we were similarly very concerned. The idea of read across
structure activity assessments are critical, but there's absolutely no justification on pulling together
this family based on the sulfates. And it's not surprising if you group every metal under 90 -- if
you group every 90 day study on a metal, that the conclusion is variable, because they are not
related. So alternatively, what one could do rather than -- we hadn't actually thought of breaking it
into six reports -- eight -- what you could do, is turn this into a metals report, and then group all
the toxicology you have on silver, all the toxicology on magnesium, all the toxicology on
aluminum, and address it from that side. But to pick the counter ion, just made absolutely no
sense, and indeed, one of our more generic comments which would be here and in the citrus
report, is that there needs to be a much more robust discussion as to why you thought the sulfate
was the driver of this family, as opposed to the metal side.

DR. MARKS: Bart, thank you.

DR. HELDRETH: Okay, so what I hear here is that read across is the only
possible rationale for grouping ingredients and I think that's absolutely false. Recently we did an
amino acids report. Did we use read across from phenylalanine to glutamine? I don't think we
did. Yet the reason we grouped those ingredients together was because it was nice to have all of
those ingredients in one place in one report. We were able to contrast those differences within the
report, why certain individuals might have problems with phenylalanine or the sodium glutamate,
whereas the other amino acids would not have an issue. The contrast does add information to the
report, to the safety and to the profile of those ingredients. So while read across is probably the
best reason to group ingredients together, I think it's not the only reason to do so. I agree that
there is a major strain trying to read across, across sulfates. But I would also conjecture that
there's some strained reading across on the other anion as well. I wouldn't read across mag
chloride to mag sulfate. So instead of looking at it as, we have to do read across here, one
potential, and it's the Panel's prerogative to decide how they want to do it, by all means, is to look
at this as putting a certain number of ingredients in one place, that a formulator could go to.

DR. ANSELL: It's just that logic that we think is missing here, that we would
love to have in these family groupings -- is exactly what you just said, as to why this made sense.
Because it's far from clear to us that grouping based on sulfate makes any sense at all. But there
are other ways of doing it -- individual metals, grouping all the data on a metal, in a report. You
just need to iterate and clarify how these reports were generated.

DR. HILL: I wasn't happy with the grouping all the amino acids together either,
by the way. In fact I was exceedingly unhappy. I wasn't even happy that CIR staff time got spent
on reviewing amino acids, and I think the logic was, well, if we're going to review proteins, we
should start with amino acids, which I think was spacious logic. That's just bink, but I'm looking
at sulfate and saying, first of all, I would read across mag chloride to mag sulfate, even though
solubility-wise, it wouldn't be quite different but -- so, again, in terms of biochemistry, grant you,
there are general ways of handling sulfate, but not much concern whatsoever about toxicology, but
on the other end, with the metals, since metals are cofactors for practically every enzyme in the
human -- well, a large number of enzymes in the human body, and they affect the operation of
many others, that puts you in a very different regime. And again, from the standpoint of entering
the body in most cases, other than maybe localized effects in mucous membranes, or inhalation
potentially comes into play, not so much in the lungs, because of respirability, but in nasal mucosa
potentially -- other than that, we're probably in most of these going to say no problem because.
But to me, convenience, or some perceived convenience does not trump the toxicology end of
what we're doing here, and when you lump things together that are so disparate both in terms of
function and physical chemical properties and chemical properties and in biochemistry, it basically
is -- it confounds, for me, any sense of being able to sort out what's really going on here. So I
have to mentally take them ingredient by ingredient in anyway. And while I appreciate that
contrasts are important, I think you can always reference back to -- okay, well there are these other
four reports and here is what we found there. You can put those contrasts into any given report, without actually putting things together, in my humble opinion. But for the review, having things that are much more related is -- makes the review much easier because you can look at the toxicology end of it. And again, I won't call myself a toxicologist -- I'm learning -- but I spend my entire life every day working -- and my wife would also say sleeping and showering and everything else -- thinking about how chemistry relates to biology because that's what I do.

DR. SHANK: I guess I'm the odd man out. At first it seemed difficult to handle all of these inorganic sulfates as one group, but when I separated them from the soluble from the insoluble, it became a lot easier. And then I thought, well okay, let's do it with the other -- with the metals. And then if you do all of the copper together, that's harder to handle than inorganic sulfates. So I like this, actually, and I had data needs for dermal penetration for the soluble sulfates and especially iron, copper, manganese, because those are all -- have known toxicities, as does sulfates. So I did not have a problem with this as a group.

DR. MARKS: Okay. Ron Hill and Tom -- do you want to comment about that and go back -- you made Bart's day. You know that Ron Shank? So you had some needs. I had some needs, too. I thought it would be an insufficient data and I noted I wanted HRPT for barium, magnesium and sodium, interestingly, even though we had sodium sulfate before it's being used at 96.8 percent. And I didn't see any HRPT for that high a concentration of use. You weren't concerned about, so obviously, Ron, I'll ask you -- Ron Shank, I'll ask you to repeat your needs since I can put diff -- we're going to proceed on with this report together. And what did you want to do about the per-sulfates? That seems like we already had a report on that. Did we --

DR. SHANK: But I didn't see the need to have --

DR. MARKS: Yes.

DR. SHANK: To have the per-sulfates in here.

DR. MARKS: Okay.

DR. SHANK: Keep it simple and make it just the sulfates.

DR. MARKS: And then would you reopen sodium then? Sulfate, include it with this, Ron Shank, or would you leave that as a standalone?

DR. SHANK: As far as I'm concerned, that's been reviewed and stands alone. So it can be referred to in here, but there's no data needs for that.

DR. MARKS: So Tom and Ron Hill -- you've heard a discussion that Ron Shank just made.

DR. SLAGA: Well I agree with Ron in terms of -- we need data on dermal absorption for all the soluble ones. I mean -- three-quarters of the report is on IP, subcu, which is really has no relevance to the skin here in this case. But that's really the only need that I would see. If we eliminated per-sulfates and the sodium sulfates.

DR. MARKS: So, and then Ron Shank, you were very specific. Dermal absorption on soluble metals, and you said specifically iron was one of them, where there some -- what were the others?

DR. SHANK: Well, dermal absorption on the soluble sulfates.

DR. MARKS: Um-hmm.

DR. SHANK: And then, with the particular attention to the iron manganese and the copper, because we are aware of significant systemic toxicity with those.

DR. MARKS: And do we -- Wilbur and I'll ask Ron -- both Ron's and Tom again -- I'm -- Bart was very elegant in his reason why he grouped them. I think that needs to perhaps occur in the discussion, so that there's some understanding of the initial blush obviously, by individual, could be why are these grouped together. And so I think there needs to be some discussion on that. So we have -- so I would say, let me see -- I'm not sure who's proposing it tomorrow. At any rate, I would say we would have to put and insuff -- present an insufficient data notice. And then I would want HRPT for barium, because it's used up to 37 percent in lipstick, manganese -- it's used up to 49 percent. The others I thought were fine. And dermal absorption on the soluble metal sulfates -- am I using that correct -- soluble metal sulfates, Ron Shank?

MR. JOHNSON: Soluble sulfates.

DR. MARKS: Soluble sulfates, okay. Iron, manganese and copper, specifically we were concerned about. Now normally, we put in the caveat, if they are absorbed, then we'll need development, repo, and all that sort of stuff, but we'll see if they're absorbed first. We can
MR. JOHNSON: Can I just ask one question, (inaudible) the decision was made to include --

SPEAKER: Can you turn your mike on please?
SPEAKER: It is.

MR. JOHNSON: Yes, the decision was made to add sensitization data on the per-sulfates, due to the absence of those data on the other ingredients that are being reviewed in this safety assessment. So, but your decision is to basically delete all of the per-sulfates data from this safety assessment?

DR. MARKS: Yes. Any other comments? Jay -- I can see there --

DR. ANSELL: I guess it's more a question, so what did we -- we're happy in grouping sub-chronic across all the metals into a single report? Do we think seeing a feeding study on aluminum informs anything about iron safety? Or --

DR. SHANK: No, we didn't say that.
DR. ANSELL: No, so I'm curious as to --

DR. SHANK: No, we're not saying we can read across from one metal sulfate to the other. On the other hand, changing this report to all the iron containing cosmetic ingredients is one report. All the copper containing ingredients in another report, is probably going to be more troublesome than taking care of the inorganic sulfates as one. Because if you do all of the coppers, you're going to have inorganic and organic. If you do all one metal by the other, so it doesn't bother me to handle the inorganic sulfates as one group. But I'm not saying there's going to be read across, all right?

DR. HILL: I'm not happy. And I think one of the reasons -- what always sticks out in my mind when we lump these things together, is I know how these reports get used in the future, so in some future report, there will be some sentence that says, "the sulfates reviewed in 1991 and were found safe in cosmetic" -- and then if you don't go back and look at the details of that report, which, I mean -- that's what's being suggested for the reader, but such a little innocent statement can mask a whole lot of detail that will come in a report where we're mixing a lot of things together like this. So that's probably what bothers me the most is -- for future usage, for future reference -- well, we reviewed the sulfates and they were all found safe. And then there are lots of provisos that don't necessarily get captured by that. I think you have things that are closely related, then such statements make a lot more sense, and while I again appreciate the usefulness of making contrasts, I'm not thinking that that's a good reason to lump things together.

DR. BERGFIELD: Are you suggesting that per-sulfates should be mentioned in this just for reference, or just --

DR. HILL: Are you talking to me?
DR. BERGFIELD: Yes, Ron Hall, I'm talking to you.
DR. HILL: Then no, other than just to say, we didn't include these --

DR. BERGFIELD: Um-hmm.
DR. HILL: And here's why. But I was still suggesting eight different groupings.

MR. JOHNSON: What is the reason why they are not being included?
DR. SHANK: Timothy here differs.
MR. JOHNSON: Dr. Hill, how would you group these then? If it's not one report, how would you group them into other reports?

DR. HILL: Well, if you want to know the specific ones that I would group, I can give you that, because I've got them color coded. If that's what you're asking.

MR. JOHNSON: Well how did you separate it into different groups.

DR. HILL: Considerable water solubility versus not -- known biological activities of metal ions versus not, known differences in the types of biological activities of those metal ions versus the others -- like that. And my biggest concerns will not be -- I think you'll find that there isn't any significant percutaneous absorption for any of these, and so my concerns are all related to things that might happen in mucous membranes, including the mouth, it's in the mouthwash, and nothing else. Or nasal mucosa, if there's -- if we have a powder or spray.

DR. BERGFIELD: And your concerned that the concentrations of use, or just the chemical?
DR. HILL: You don't need a very high concentration of certain of these to potentially have effects in the context of mucosa and the like, whereas others, you could have a ton of it and you'll never get any toxicity, other than unless somebody's drowning in a vat of powder.

DR. MARKS: Okay, so the only other thing I'd mention Wilbur, is we should have the inhalation boiler plate, since some of these ingredients will be -- if I -- maybe I missed that in this draft report. Is that correct, Ron -- Ron Shank? Did you mention that -- the inhalation boilerplate?

DR. SHANK: I didn't mention that, no. But I agree with you.

DR. MARKS: Okay, so tomorrow, let me see -- I'm going to either propose -- let me see here, yes. So, I'm going to make a motion that an insufficient data notice be issued, that we need the HRIPT for barium, manganese and the dermal absorption for the soluble sulfates, specifically iron, manganese and copper. There will be a discussion I'm sure, on grouping these inorganic sulfates together. Bart may be called on again. Ron, I'll have you discuss your reasoning and then, Ron Hill -- you'll have an opportunity to counter and obviously Jay, and PCPC also can. Rachel, did you have any comments? Okay. Good.

MR. JOHNSON: Excuse me, Dr. Marks. The inhalation boiler plate is on page 11.

DR. MARKS: Okay, great, thank you.

MR. JOHNSON: You're welcome.

DR. MARKS: I missed that.

DR. GILL: And Jim, just to be clear, we are removing all of the per-sulfates.

DR. MARKS: Yes. Actually we're removing sodium sulfate and the three per-sulfates that had been previously removed, or previously reviewed and concluded on. Okay. Any other comments about the inorganic sulfates? Thanks, Wilbur.
Day 2 of the March 17-18, 2014 CIR Expert Panel Meeting – Full Panel

**Barium Sulfate**

The inorganic sulfates. Dr. Marks?

DR. MARKS: This is the first review of this draft report. There are 17 inorganic sulfate ingredients. Our team, after discussion, felt that we could delete the persulfates. They've already been previously reviewed as to what is sodium sulfate. And we could move forward with an insufficient data notice. We want an HRIPT for barium magnesium and dermal absorption on soluble sulfates of iron, magnesium, and copper. We had a pretty robust discussion of whether or not this ingredient grouping was the right one. We decided to move forward. There were some differing opinions among our team but we decided to move forward with the ingredient grouping as presented, the inorganic sulfates.

DR. BERGFELD: And that's a motion?

DR. MARKS: So the motion is an insufficient data notice and the needs are what I said -- HRIPT for barium magnesium and dermal absorption for the soluble sulfates -- iron, magnesium, and copper.

DR. BERGFELD: Dr. Belsito's team?

DR. BELSITO: Well, we had a quite different opinion. This is a group that we thought was grouped the wrong way. First of all, the persulfates don't belong in this group at all, so we agree that they be removed. However, it's not the sulfate that wags the tail of this group; it's the metal salt. And so we felt this grouping made absolutely no scientific sense. Having said that, we felt that it did make sense to look at the two high volume ones -- magnesium and barium. You know, magnesium sulfate is used, for those of you who have had colonoscopies as an agent that you take internally before the colonoscopy. Barium sulfate is used for performing barium enemas and other types of swallows. So there's a huge amount of medical safety data. I've been testing both of those metals in my metal panel for over 30 years and have never seen a sensitization reaction, so I'm really not concerned about an HRIPT. And we felt that we would eliminate everything except magnesium and barium sulfate and go with a safe as used for them.

DR. SHANK: As individual reports?

DR. BERGFELD: Ron Shank?

DR. BELSITO: As individual reports. Right.

DR. BERGFELD: Halyna?

DR. BRESLAWEC: Yeah. This is an issue that the Council and the CIR Science and Support Committee is very, very concerned about, and that is providing a reliable and robust justification for grouping of compounds that are -- ingredients that are reviewed together. We agree with Dr. Belsito's assessment that this grouping was not -- is not supportable, and we just want to really make clear as we go ahead and look into 2015 and future priority-setting that there is a sound justification for grouping, whether it's you're grouping for chemical similarities to provide for read across; you're grouping for similar functions or similar uses; you're grouping for similar chemical properties; or even you're grouping for something a little more creative as we've been known to do. And that's fine. But you have to have the sound justification for grouping, and we did not believe that this group had such.

DR. MARKS: So that was exactly our discussion. I would ask Ron Shank and Bart to comment on the grouping.

DR. BERGFELD: Ron, do you want to lead off?

DR. SHANK: It didn't bother me to put these all together. I realize sulfate is not the toxicological driver in this, but chemically, they are a group, inorganic sulfates. And I separated them based on solubility. Soluble and nonsoluble, and that made it much easier to handle.

We also discussed looking at the metal. Actually, that makes it much more difficult if you take all copper compounds and you have a worse grouping than this. So I was not appalled by having this as a group, and I could handle it, especially if I did it by soluble and nonsoluble. And I don't care about the enemas.

(Laughter)
DR. BERGFELD: Ron Hill, did you have a comment?

DR. HILL: Yeah. I mean, I was not with the consensus of this side and much more in line with what you were talking about, and I suggested a minimum of eight groupings. Well, a minimum of eight groupings for this. I had color coded them in the table as to how I came up with that.

DR. BERGFELD: Tom?

DR. SLAGA: I agree with Ron.

DR. BERGFELD: You agree with Ron?

UNIDENTIFIED SPEAKER: Which Ron?

DR. BERGFELD: Which one?

DR. MARKS: Let the record show Tom says he agrees with Ron Shank.

DR. BERGFELD: Dan?

DR. LIEBLER: I essentially agree with -- the position of our group as Don has enumerated it.

DR. BERGFELD: Paul?

DR. SNYDER: Yes. I think we came to the conclusion that if we split them out into individual reports with the barium and magnesium, we can actually have enough data to go safe as used with what's in the document already.

DR. SHANK: What are you going to do with all the others? All the other sulfates that are here?

DR. BELSITO: Most of them aren't used. They fall off our priority list.

DR. BERGFELD: So you delete them from the ingredient group?

DR. BELSITO: We actually want to follow, as Halyna said, a sensible approach where the metal is the driving factor and actually take these and do two reports -- barium sulfate and magnesium sulfate. Not together, two separate reports. And then see where all the other sulfates fall on our priority list, which is probably going to be way down at the bottom.

DR. BERGFELD: So, Jim?

DR. MARKS: I think Bart should comment, too.

DR. BERGFELD: Bart?

DR. HELDRETH: I think Dr. Shank made my point better than I could.

DR. BERGFELD: So Dr. Marks?

DR. MARKS: I think it's -- whether we go back to doing individual ingredients or whether we can do groups, I certainly agree with Dr. Ron Shank about we can't divide them up into metals. So I think it's a question of can you do the sulfates together or do one individual -- the magnesium sulfate, barium sulfate. And as you said, Don, the others aren't used so you can ignore them.

DR. BELSITO: But how can you ignore them? I mean, so silver sulfate isn't used. You know, so are we going to say that it's insufficient? Or are we going to go out and get all the data on silver sulfate? I don't think it's such a big problem. I agree with what Ron Shank said. There will probably be a lot of other uses for copper that come along that aren't as simple as a sulfate salt. But these are very quick reviews as individual ingredients. And if we feel we need to look at, you know, we could add copper sulfate to look at the toxicity of copper. If it's going to be released from an ingredient, that it also contains copper. I mean, we can add that to that ingredient at some point, but it just, you know, when you're grouping, our idea when we talked about grouping was that you can read across. You cannot read across the safety or barium to the safety of silver. So the group makes no sense as we defined the way we're going to group.

DR. BERGFELD: Halyna and then Ron.

DR. BRESLAWEC: Yeah, again, I would like to remind the panel that the reason that this group came together is that there were two ingredients that had high usages and those were magnesium sulfate and barium sulfate. And once you had those two ingredients, then there was an attempt, I think, to see if you could expand it to a larger grouping. And it's the panel's decision whether they feel it's appropriate to expand or just to focus on the barium and the magnesium, which are the ones with the high usages which brought them onto the priority list.

DR. BERGFELD: Ron Hill?

DR. HILL: And I want to make further comment because the priority list is up to 2015. My comments yesterday focused on the biological functions of metals because sulfate, to
my knowledge, other than organic sulfations and metabolism doesn't have such functions but metals, many of these that show up there are in cofactors and enzymes. That's not an issue if they don't get into an organism, so I brought up mucous membranes of any kind, including nasal mucosa. And then the other thing I didn't bring up yesterday was if they have redox properties that means they can do things like catalyze oxidations. And so in terms of safety review, anything that might happen in a formulation, we don't review formulations, but we can review what the potential impacts of the element has in formulations. So if you look at silver, an easy conversion between silver one and silver two oxidation state and that means it can both reduce and oxidize. Some of these others are similarly, and anything that relates to that that might come up in terms of potential, like when we consider penetration enhancement. In this case it would be possible effects in formulation that might need to be pointed out in the context of a report. And so that's why I came up with somewhere in the order of eight different groups because the metal drives the chemistry here, not the sulfate. And grouping just for convenience of sulfate, all right, these are inorganic sulfates purportedly but then we have hydroxylamine in there, so why not morphine sulfate? I mean, I'm being facetious but --

DR. BERGFELD: Dr. Marks, do you want to restate your position or change it?

DR. SHANK: Well, if you're going to throw out most of the compounds on the list you've changed the argument. You've taken a list of I don't remember how many there are -- 15, 17, 18 compounds -- and you're throwing away, taking off the list, most of them with only two left. That's an entirely different argument. If we have to handle them all together, that's one thing. If we only have to handle two, then we would handle the two in one report or will each one be a separate report?

DR. BELSITO: There will be two short, very separate reports, safe as used.

DR. SHANK: Not considering the rest?

DR. BELSITO: Not considering the rest and putting them back and see where they fall on the priority list, which will probably be way at the bottom when you look at the other reported number of uses.

DR. SHANK: Is that acceptable, Dr. Gill?

DR. HILL: To me it's acceptable. Yes.

DR. SHANK: I asked Dr. Gill.

DR. BRESLAWEC: The other Dr. Gill. Listening to both sides of the panel discussion, certainly regroup for reasons other than read across is my understanding. And for me, if I hear the argument -- and I'm willing to accept the argument and do separate reports -- however, I think we still retain the right to group for things other than read across where there is good and justifiable reason. And we would make the explanation for those. So in this case, Dr. Shank, it is okay with CIR.

DR. BERGFELD: Any other comments? Dr. Marks?

DR. MARKS: Yeah. So I withdraw the motion for insufficient data notice and our team will support the way to move forward as you suggested, safe for barium magnesium. I must point out I don't see any irritation or sensitization data for these two, and even though I know anecdotally experiences that we don't see, either irritant or allergic contact dermatitis, I think we should have some data at least to support that. It's used in -- barium is used in 37 percent use concentration. Lipstick, you would think at least there's one lipstick out there containing this that has some sensitization data, and magnesium is used up to 49 percent.

And just to comment, Don, in terms of patch testing these metals, there can be irritants in patch testing.

DR. BELSITO: Yeah. You can say when formulated to be nonirritating. I don't have an issue with that. But, I mean, the fact that they're used at those concentrations, we've used that argument before and there are no clinical reports, you know. And if you want, I can run the number of metal panels that I've run with these ingredients and tell you that I've had no reactions to barium or magnesium in the years that I've been testing.

DR. MARKS: I think that would be very good, actually. That gives us some hard data.

DR. BERGFELD: I'd like to comment on the status of this particular report. Now, it's been agreed -- we haven't quite voted on it -- that we would go the route Dr. Belsito is suggesting, two separate reports on the barium and magnesium.
What I'd like to ask Lillian Gill is would this be a tabled document so this could happen or would we move forward with these two documents without the panel seeing them for a final? It seemed to me it would be a tabled report.

DR. GILL: I think we move forward with two separate reports. I thought I heard safe.

DR. BELSITO: Yes.
DR. GILL: And we will bring them back one more time for review.

DR. BERGFELD: Okay. So you need no action other than a motion to separate them in this manner, to two separate reports?

DR. GILL: Yes.
DR. BERGFELD: Okay. Because we just earlier did something similar. We tabled it to reorganize, but you don't feel that this is necessary here?

All right. Just clarification. So, Don, will you restate your motion and we'll call for the vote?

DR. BELSITO: Two separate reports, magnesium -- yes, Wilbur?

DR. JOHNSON: Is this conclusion safe as used or is it safe when formulated to be nonirritating or safe as used --

DR. BELSITO: Safe as used when formulated to be nonirritating.

DR. JOHNSON: Okay, thank you.

DR. BERGFELD: Continue, Don.
DR. SHANK: For which two?

DR. BELSITO: Magnesium and barium.

DR. MARKS: So I'll second that. This would go out as a tentative report with conclusions. It would go out as two tentative reports with the same conclusions -- formulate to be nonirritating.

DR. BERGFELD: For clarification, this would come back first to us before it goes out?

DR. BELSITO: It's a tentative final. We'll see it as a final.

DR. BERGFELD: Okay. One other question.

DR. JOHNSON: Dr. Belsito, will you be providing CIR with actual data that would need to be incorporated prior to issuance of the report?

DR. BELSITO: I will tell you the number of patients that I tested to my metal panel and I will tell you -- so I will give you a denominator and I will give you a numerator as to the number of patients who reacted. I believe that numerator will be zero.

DR. JOHNSON: Okay. Thank you.

DR. MARKS: And I would also ask Industry to go back and see if there aren't HRIPT on these.

DR. BRESLAWEC: I'm glad to do that and I'm sure we can find something.

DR. HILL: The thing is the barium sulfate I think is a rock, so we emphasize the very, very, very, very, very low solubility if I'm not mistaken. That would explain any lack of

DR. BERGFELD: Thank you for that. We'll move the question then. All those in favor of two tentative final reports, please raise your hands. Unanimous. Thank you.
Safety Assessment of Barium Sulfate as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: May 16, 2014
Panel Date: June 9-10, 2014
ABSTRACT: Barium sulfate functions as an opacifying agent in cosmetic products, and is being used at concentrations up to 0.99% and 37% in rinse-off and leave-on products, respectively. The Panel noted that the history of safe medical use of barium sulfate indicates no significant toxicity concerns relating to systemic exposure to this ingredient. Furthermore, the extensive clinical experience of the Panel, including the results of numerous patch tests, indicates that barium salts do not have the potential to induce sensitization. The Panel noted that salts of sulfuric acid, such as sodium sulfate, can be irritating to the skin, so cosmetic products containing barium sulfate should be formulated to be non-irritating. The Panel concluded that barium sulfate is safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating.

INTRODUCTION

The safety of barium sulfate, an inorganic sulfate, as used in cosmetics is reviewed in this safety assessment. Barium sulfate functions as an opacifying agent in cosmetic products.

CHEMISTRY

Definition and Structure

Barium sulfate (CAS No. 7727-43-7) is the inorganic salt that conforms to the formula that is included in Figure 2 below. It is the barium salt of sulfuric acid.

\[ \text{BaSO}_4 \]

Figure 2. Formula for Barium Sulfate

Physical and Chemical Properties

Barium sulfate, available in the form of polymorphous crystals, has a molecular weight of 233.39, and is soluble in sulfuric acid, but insoluble in water.

Method of Manufacture

Barium sulfate may be produced by treating a solution of barium salt with sodium sulfate (salt cake).

Composition/Impurities

Barytes is the naturally occurring rock form of \( \text{BaSO}_4 \). A study was performed to characterize the mineralogical forms of barium and the trace heavy metal impurities in commercial barytes of different origins using electron probe microanalysis (EPMA), X-ray diffraction (XRD), and inductively coupled plasma mass spectrometry (ICP-MS). Qualitative EPMA results indicated the presence of different minerals in commercial barytes, including barite (\( \text{BaSO}_4 \)), barium feldspar, galena (\( \text{PbS} \)), pyrite (\( \text{FeS}_2 \)), sphalerite (\( \text{ZnS} \)), quartz (\( \text{SiO}_2 \)), and silicates. Quantitative EPMA confirmed that the barite crystals in the barytes contain some strontium and a little calcium, whereas, trace heavy metals occur in the associated minerals. Analysis of \textit{aqua regia} extracts of barytes samples by ICP-MS has indicated the presence of a large number of elements in the associated minerals. Arsenic, copper, and zinc concentrations correlate closely in all 10 samples.

Chromium has been detected in commercial samples of pharmaceutical grade barium sulfate at concentrations ranging from 0.45 to 1.06 µg/g.

USE

Cosmetic

Barium Sulfate functions as an opacifying agent in cosmetic products.
According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), barium sulfate is being used mostly in leave-on products. Results from a survey of ingredient use concentrations provided by the Personal Care Products Council in 2013 indicate that this ingredient is being used at concentrations up to 0.99% (in skin cleansing products - rinse-off products) and 37% (in lipsticks - leave-on products). Summarized data on frequency and concentration of use in cosmetics are presented in Table 1.

Cosmetic products containing barium sulfate may be applied to the skin and nails, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Barium sulfate is being used at concentrations up to 15% in cosmetic products that are sprayed (perfumes) and at concentrations up to 15.8% in powders (face and dusting powders). Because this ingredient is used in aerosol/pump hair sprays and in powders, it could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump spray. Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.

Non-Cosmetic

There are a number of indirect food additive uses for which barium sulfate has been approved. Barium sulfate has been used as a gastrointestinal contrast agent in roentgenographic procedures. Barytes (the naturally occurring rock form of BaSO₄) has been referred to as the standard densification agent used in drilling fluids worldwide.

TOXICOKINETICS

Rats inhaled barium sulfate at concentration of 40 mg/m³, 5 days per week (5 h/day) for up to 2 months. The rats were killed at 2-week intervals after the beginning of the exposure period, and the barium content of the lungs, lymph nodes, jaw, and femur was determined. Lymph transport was negligible. The barium content of bone increased initially, and then gradually decreased during treatment. After 2 weeks of exposure, the barium content of the lungs was high, but decreased rapidly and then increased considerably over the next 4 weeks of treatment.

Following endotracheal administration of barium sulfate (Baropaque™) into 220 Sprague-Dawley rats and 3 dogs, radiographic and histologic studies were performed. Baropaque™ (0.25 ml), under fluoroscopic control, was injected endotracheally into rats, and a 1.75 ml/kg dose of Baropaque™ was administered endotracheally to dogs. The 0.25 ml dose was selected based on the results of a pilot study in which all 30 rats died after intratracheal administration of 0.5 ml Baropaque™. After dosing with Baropaque™, all of the rats and 2 dogs were radiographed for a total of 9 months. Baropaque™ was virtually cleared from the trachea and stem bronchi in 30 minutes. Baropaque™ cleared more slowly from the lungs of 3 dogs, when compared to these data on rats. Additional study results are included in sections on Acute Intratracheal Toxicity and Inflammatory Response.

TOXICOLOGY

Acute Toxicity

Oral

Six groups of 16 to 26 young male CBL-Wistar albino rats (ages not stated) received the following 6 total doses of barium sulfate (150% w/v suspension), respectively, by intragastric cannula: 188, 225, 263, 300, 338, and 375 g/kg. For each total dose, 40% was given initially, followed by 35% of the dose 3 h later, and 25% 4 h later. Fifty control rats were dosed with distilled water. Fifty experimental animals died from stomach rupture, and the mean LD₅₀ was 307 ± 29 g/kg.
Stomach rupture appeared to have been due, in part, to failure of the animal to pass barium sulfate along the gastrointestinal tract. In 90% of the animals, hemorrhagic areas were found in the gastric mucosa, mainly on the anterior and posterior surfaces. The adrenal glands were enlarged, the liver was small, and the stretched abdominal muscle had a watery consistency.

**Intratracheal**

Following endotracheal administration of barium sulfate (Barosperse™) into 220 Sprague-Dawley rats and 3 dogs, radiographic and histologic studies were performed. Barosperse™ (0.25 ml), under fluoroscopic control, was injected endotracheally into rats, and a 1.75 ml/kg dose of Barosperse™ was administered endotracheally to dogs. The 0.25 ml dose was selected based on the results of a pilot study in which all 30 rats died after intratracheal administration of 0.5 ml Barosperse™. After dosing with Barosperse™, all of the rats and 2 dogs were radiographed for a total of 9 months. Diffuse, but patchy, acinar filling resulted in a slow decrease in barium aggregates from the lungs of rats and dogs over a 9-month period. New infiltrates were found in 15% of the rats on serial follow-up. Two of the 3 dogs dosed with Barosperse™ died during the first 24 h; both dogs had diffuse alveolarization of the contrast agent.

**Inflammatory Response**

**Inhalation**

Groups of male Wistar rats were exposed (whole-body) 5 days per week (7h/day) to barium sulfate dust. At each of 6 time points, 12 rats were drawn, 6 for bronchoalveolar lavage (BAL) and 6 for dust burden measurements. Of the 6 time points included in the protocol, only the following 4 were clearly defined: 42 days, 50 days, 70 days, and 90 days. Animals destined for bronchoalveolar lavage studies were killed 18 h after completion of the final day of exposure for that time point. Considering that dust deposited higher in the respiratory tract would have time to clear, animals used for lung and dust burden analyses were killed 66 h after the end of exposure. Three age-matched sham-exposed animals were used as controls at each time point for each test condition in the lavage studies.

The results of BAL fluid analyses indicated that: the time course of neutrophil recruitment during exposure to barium sulfate resembled that of lymph node burden; barium sulfate dust produced a low degree of inflammation at the last 3 time points of the higher (75 mg/m³) exposure concentration; the mean numbers of alveolar macrophages did not change significantly when compared to the background level in control animals; and animals exposed to barium sulfate dust had significantly higher numbers of lymphocytes in BAL fluid when compared to controls.

Histological sections from animals killed at timepoint 6 indicated that inhalation of barium sulfate elicited accumulation of pulmonary macrophages around the dust deposition sites. The highest concentrations of macrophages with phagocytosed dust were at the bifurcations of the terminal airways and bronchioles. In some cases, there was an accumulation of inflammatory cells, including fibroblasts in the interstitium. Some macrophages with their dust burdens had become interstitialized as well, with the lesions becoming microgranulomas. In most cases where centriacinar macrophage aggregations were found, the walls of surrounding alveoli appeared thickened, mainly due to the rounding of epithelial cells, indicative of Type II cell hyperplasia. Barium sulfate did not show significant fibrogenic activity in this study.

**Subcutaneous**

The effect of intrauterine, s.c. injection of sterile barium sulfate into rabbit fetuses was evaluated. Healthy pregnant rats (number not stated) of gestational periods ranging from 21 to 26 days were used. Two fetuses were selected at random. The dorsum of the fetus was delivered and a sterile aqueous suspension of micro-opaque barium sulfate was injected into the subcutaneous tissue of each dorsolateral surface. The hysterotomy wounds were then closed. The pregnancy was allowed to progress and fetuses were removed at varying postoperative intervals for morphological studies. Similar s.c. injections were performed in newborn rabbits. The rabbits were killed at regular intervals and the morphology of the wounds was studied. Subcutaneous injection of sterile barium sulfate in newborn rabbits produced an acute inflammatory response that was observed clearly at 24 h and well-established by 48 h. The process of repair had begun by day 4, whereby the appearance of proliferating capillaries and fibroblasts was observed. Both vascular and cellular components of the acute inflammatory response were more prominent in rabbit fetuses, and appeared earlier (well-developed within 24 h) when compared to newborn rabbits. The process of repair also began earlier; the proliferation of capillaries and fibroblasts was prominent by 48 h. By day 4, the lesion was compact, less cellular, and relatively avascular.
Endotracheal

Barium sulfate (Baropurse™) was administered endotracheally into 220 Sprague-Dawley rats and 3 dogs.19 Barium in the alveoli and a mild acute inflammatory response were observed in rats at microscopic examination. A few hours after instillation, macrophages were observed in the alveoli and subsequently became evident in thickened septa. Focal alveolar wall granulomata were also observed. After 3 months, focal areas of acute and chronic inflammatory cells with focal fibrosis persisted, and areas of atelectasis and emphysema were also observed. At 6 months, aggregates of macrophages containing barium were the main finding. At 9 months, nodules of phagocytic cells in bronchioles and perivascular structures persisted. At 9 months after Baropurse™ instillation into the lungs, the same histological findings were observed in 3 dogs.

Case Reports

Exposure to barium sulfate occurs in miners of barium and its salts, workers in the lithopone industry, and in patients undergoing diagnostic roentgenography of the gastrointestinal tract.23 Barium sulfate dust, when inhaled, leads to a benign form of pneumoconiosis (baritosis), which occurs primarily in miners and workers in the lithopone industry. Escape of barium sulfate from the digestive tract into the peritoneal cavity has been reported in patients with peptic ulcers undergoing x-ray studies. Barium granulomas have been reported in the appendix, sigmoid and peritoneum, and rectum in patients receiving barium enemas.

A 43-year-old patient was diagnosed with acute appendicitis, and barium sulfate was used in diagnostic studies, i.e., upper gastrointestinal series and barium enema.23 During these procedures, barium sulfate entered the appendix and escaped into the mesoappendix and adjacent periappendical fat. The resulting foreign-body granuloma was said to have been due to the escape of barium sulfate.

A case of barium sulfate-granulomatosis of the lung was reported for a 67-year-old man, due to barium sulfate aspiration during an x-ray investigation of the stomach.24 In the lung parenchyma, multiple granulomas were observed in groups of alveoli where barium sulfate had been deposited.

Barium enema examination is a frequently performed radiographic procedure, and this procedure was reported to caused barium granuloma of the rectum in 2 patients (males 75 and 78 years old).25 Rectal intramural extravasation of barium occurs as a result of asymmetric enema balloon inflation and impaction of the enema tip against the rectal mucosa. The lesions appeared as indurated, ulcerated rectal masses that resembled carcinoma on endoscopic examination. Deep mucosal biopsy results demonstrated no malignancy or barium sulfate crystals in tissue macrophages. Radiographs showed persistent soft-tissue barium in the rectum.

A severe anaphylactic reaction was observed in a 51-year-old female cancer patient at approximately 5 to 10 minutes after starting a barium enema.26 The barium enema mixture contained barium sulfate, sodium benzoate, potassium sorbate, citric acid, sodium saccharin, ethyl maltol, vegetable gum, sorbitol, simethicone, and natural and artificial flavors. It was stated that the anaphylactic reaction could have been an IgE-mediated hypersensitivity reaction to one of the barium sulfate suspension constituents. The patient had a history of prior sensitizing exposure to barium radiographic contrast material. No skin prick test reaction, i.e., no cutaneous hypersensitivity, to diluted sodium benzoate, potassium sorbate, or whole liquid barium sulfate suspension was detected. The patient declined further provocation testing. The authors noted that the patient’s severe reaction to barium may have been partly attributable to the following 3 factors: (1) her history of atopy and prior medication allergy, (2) a prior sensitizing exposure to barium sulfate, and (3) possible increased absorption of allergens into the bloodstream through the recurrently bleeding ulcerated carcinoma of the sigmoid colon.

Two children developed hypersensitivity reactions of varying severity following upper GI series.27 The first case involved an 11-year-old boy with documented anaphylaxis, following exposure to fish and peanuts, and multiple food intolerances. The patient experienced oral swelling and a red swollen tongue after drinking 150 ml of 45% weight/weight barium sulfate. The absence of sequelae after prior upper GI series that involved drinking barium sulfate was noted. Endoscopic biopsies from the upper and lower GI tracts established the diagnosis of eosinophilic gastroenteropathy. The second case involved a 7-year-old girl with a history of mild allergy to penicillin (hives), but no other known allergies. After drinking 150 ml of 45% barium sulfate, she developed urticaria on her face, trunk, and lower extremities.

Cases of patients with a “magenta colon” from radiologic barium have been reported every 3 to 4 years.28 This condition can occur with either upper or lower barium contrast studies, resolves over 4 to 7 days, and can be present without visible residual barium. It was noted that most reactions are mild, but, occasionally, are severe enough to hamper determining whether there is true colitis. The severe reaction is characterized by edema, loss of all vascular markings, and
redness to almost a magenta color, but without ulcerations, friability, necrosis, or exudate. Biopsies show inflammatory changes.

**GENOTOXICITY**

**Barium Sulfate**

The genotoxicity of barium sulfate was evaluated using murine fibroblasts in the *in vitro* single-cell gel (comet) assay. The fibroblasts were exposed for 5 h (at 37°C) to barium sulfate at final concentrations ranging from 10 to 1,000 µg/ml. Vehicle control cultures were exposed to phosphate-buffered solution, and positive control cultures were exposed to 10 µM hydrogen peroxide. A total of 50 randomly captured comets per treatment (25 cells from each slide) were examined using a fluorescence microscope. Barium sulfate did not increase cell mortality and was not genotoxic, i.e., did not induce DNA breakage. The positive control caused a significant increase \( P = 0.02 \) in tail moment, when compared to the negative control. Barium sulfate (1 to 1,000 µg/mL) also was not genotoxic in human peripheral blood lymphocytes in the *in vitro* single-cell (comet) assay.

**SUMMARY**

Barium Sulfate functions as an opacifying agent in cosmetic products. According to information supplied to the FDA by industry as part of the VCRP in 2014, barium sulfate is being used mostly in leave-on products. Results from a survey of ingredient use concentrations provided by the Personal Care Products Council in 2013 indicate that this ingredient is being used at concentrations up to 0.99% (in skin cleansing products - rinse-off products) and 37% (in lipsticks - leave-on products).

The inorganic sulfates are typically manufactured by mining of natural minerals (as many inorganic sulfates occur naturally in hydrated form) or by reaction of available ore or inorganic oxides, hydroxides, or carbonates, with sulfuric acid. These methods produce hydrated inorganic sulfates. To produce the anhydrous salts, an additional step of dehydration (e.g., by heating and reduced pressure) must occur.

Chromium has been detected in commercial samples of pharmaceutical grade barium sulfate at concentrations ranging from 0.45 to 1.06 µg/g.

Rats inhaled barium sulfate (40 mg/m³) for up to 2 months, and barium was detected in the bone and lungs. Lymph transport was said to have been negligible. Following endotracheal administration of barium sulfate (Barosperse™) into rats (0.25 ml volume) and dogs (1.75 ml/kg dose), the test material was virtually cleared from the trachea and stem bronchi in 30 minutes. Barium was detected in the alveoli at microscopic examination. Groups of young male CBL-Wistar albino rats received a 150% w/v barium sulfate suspension orally at doses up to 375 g/kg. A mean LD₅₀ of 307 ± 29 g/kg was reported.

Following endotracheal administration of barium sulfate (Barosperse™, 1.75 ml/kg dose), 2 of 3 dogs died during the first 24 h. Diffuse alveolarization of the test material was observed in both dogs.

Subpannicular injection of sterile barium sulfate in newborn rabbits produced an acute inflammatory response that was observed clearly at 24 h and well-established by 48 h. Following endotracheal administration of barium sulfate (Barosperse™) into rats (0.25 ml volume) and dogs (1.75 ml/kg dose), a mild acute response and a chronic inflammatory response were observed. In another study, groups of Wistar rats were exposed repeatedly to barium sulfate dust for up to 90 days. Barium sulfate dust produced a low degree of inflammation at an exposure concentration of 75 mg/m³.

Barium sulfate dust, when inhaled, leads to a benign form of pneumoconiosis (baritosis), which occurs primarily in miners and workers in the lithopone industry.

Barium sulfate-granulomatosis of the lung, appendix, and other tissues has occurred during radiographic procedures. Additionally, though rare, hypersensitivity reactions have been reported after radiographic procedures that involve dosing with barium sulfate.
Barium sulfate was not genotoxic to murine fibroblasts or human peripheral blood lymphocytes in the *in vitro* comet assay.

**DISCUSSION**

The Panel noted that the history of safe medical use of barium sulfate indicates no significant toxicity concerns relating to systemic exposures to these ingredients. Furthermore, the extensive clinical experience of the Panel, including the results of numerous patch tests, indicates that barium salts do not have the potential to induce sensitization. The Panel noted that salts of sulfuric acid, such as sodium sulfate, can be irritating to the skin, so cosmetic products containing barium sulfate should be formulated to be non-irritating. Barium sulfate is being used in leave-on products (lipsticks) at concentrations up to 37%.

Barium sulfate is being used at concentrations up to 15% in cosmetic products that are sprayed (perfumes) and at concentrations up to 15.8% in powders (face and dusting powders). The Panel discussed the issue of incidental inhalation exposure from propellant and pump sprays and powders, and considered pertinent data indicating that incidental inhalation exposures to this ingredient in such cosmetic products would not cause adverse health effects. The data considered include data characterizing the potential for this ingredient to cause acute toxicity, inflammation, and genotoxicity. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols 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. 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](http://www.cir-safety.org/cir-findings).

**CONCLUSION**

The CIR Expert Panel concluded that barium sulfate is safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating.
**Table 1.** Frequency and Concentration of Use According to Duration and Type of Exposure for Barium Sulfate.  

<table>
<thead>
<tr>
<th>Duration of Use</th>
<th># of Uses</th>
<th>Conc. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Totals/Conc. Range</strong></td>
<td>398</td>
<td>0.001-37</td>
</tr>
<tr>
<td><strong>Duration of Use</strong></td>
<td></td>
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<tr>
<td>Leave-On</td>
<td>385</td>
<td>0.001-37</td>
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<tr>
<td>Rinse off</td>
<td>4</td>
<td>0.0035-0.99</td>
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<td>Diluted for (bath) Use</td>
<td>NR</td>
<td>0.94</td>
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<tr>
<td><strong>Exposure Type</strong></td>
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<tr>
<td>Eye Area</td>
<td>98</td>
<td>0.01-18.6</td>
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<tr>
<td>Incidental Ingestion</td>
<td>87</td>
<td>0.04-37</td>
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<tr>
<td>Incidental Inhalation-Sprays</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Incidental Inhalation -Powders</td>
<td>43</td>
<td>0.034-15.8</td>
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<tr>
<td>Dermal Contact</td>
<td>235</td>
<td>0.0035-20</td>
</tr>
<tr>
<td>Deodorant (underarm)</td>
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<td>NR</td>
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<tr>
<td>Hair - Non-Coloring</td>
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<tr>
<td>Hair-Coloring</td>
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<tr>
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<tr>
<td>Mucous Membrane</td>
<td>88</td>
<td>0.04-37</td>
</tr>
<tr>
<td>Baby Products</td>
<td>NR</td>
<td>NR</td>
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</table>

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on Product Uses.  
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.
References


### 2014 FDA VCRP Data

**Barium Sulfate**

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<thead>
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<th>Code</th>
<th>Category</th>
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<tr>
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<tr>
<td>03B</td>
<td>Eyeliner</td>
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<tr>
<td>03C</td>
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<td>03F</td>
<td>Mascara</td>
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<td>Powders (dusting and talcum, excluding aftershave talc)</td>
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<td>Nail Polish and Enamel</td>
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**Total** | **389**
Memorandum

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

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

DATE: April 17, 2014

SUBJECT: Comments on the Tentative Report: Safety Assessment of Barium Sulfate as Used in Cosmetics

Key Issues
The Introduction should note that there is a submission to ECHA concerning Barium Sulfate that relies on data on barium chloride to support the safety of Barium Sulfate. Although details of the barium chloride studies do not need to be added to the CIR report, acknowledging the ECHA submission would suggest that the search for information was thorough, and it would provide the reader seeking more information on barium an additional source.

Additional Comments
p.1, Abstract - As there is only one ingredient in this report, the Abstract should not say “these ingredients”.
p.1 - Please add the CAS number for Barium Sulfate to the Chemistry section. As there is only one ingredient in this report, it is not necessary to provide the general information about inorganic sulfates. One figure showing Barium Sulfate would be sufficient.
p.1, 5 - The method of manufacture for Barium Sulfate should be described (rather than a general method and the description of how Magnesium Sulfate is made).
p.2, 5 - Please delete “in 2014” from the description of the use information. The information came from FDA in 2014, it was not provided by industry in 2014.
p.2, 5, 6 - As the assumptions concerning FDA product categories are not always correct, please state the specific FDA product categories associated with the maximum use concentrations in the Cosmetic Use section, the Summary, and Discussion; e.g., 0.99% in skin cleansing products and 37% in lipstick.
p.2 - In the Non-Cosmetic Use section, it should also be noted that Barium Sulfate has been approved for a number of indirect food additive uses (see 21CFR175.105, 21CFR176.170, 21CFR177.2600 and 21CFR178.3297).

p.2 - How may hours/day, days/week were the rats exposed to Barium Sulfate in reference 13?

p.2, 3 - In the description of reference 16, it is not clear what is meant by: “all of the rats and 2 dogs were radiographed for a total of 9 months”. What was the frequency the animals were radiographed during the 9 month period, e.g., daily, weekly, monthly?

p.3-4 - It is not necessary to have a separate Inflammatory Response subsection. The studies in this section should be in a section (Acute or Repeated Dose) based on the exposure duration.

p.3 - As some time points were defined “(all not specified)” should be deleted.

p.4-5 - The case reports (references 21 and 22) of anaphylactic reactions to medical use of Barium Sulfate are not relevant to cosmetic use and should be deleted from the report. If these cases are left in the report, the following report (abstract attached) that suggests that carboxymethylcellulose in the formulation may the cause of the reaction in some cases, should be added to the CFR report.


p.6 - As there are some inhalation exposure data summarized in the report, this information should be mentioned in the discussion of potential inhalation exposure to Barium Sulfate from use in spray and powder products.
Pre-lethal anaphylaxis to carboxymethylcellulose confirmed by identification of specific IgE--review of the literature.

Dumond P¹, Franck P, Morisset M, Sainte Laudy J, Kanny G, Moneret-Vautrin DA.

Abstract

BACKGROUND: Carboxymethylcellulose (CMC) is used extensively in the pharmaceutical and food industries on account of its various properties. Anaphylactic reactions are rare. It has been reported principally after intra-articular infiltration of sustained-release corticosteroids containing CMC and, very rarely, after barium enema.

METHODS: A case of pre-lethal anaphylactic shock after barium enema was studied by prick-test, intra-dermal reaction (IDR), leukocyte histamine release test (LHRT), basophil activation test (BAT), cystein-leukotriene release test (CAST) and dot-blot analysis.

RESULTS: IDR to CMC was positive at a concentration of 10 microg/ml. BAT and CAST were positive. Specific IgE were identified using dot-blot analysis.

DISCUSSION: This is the third report of CMC-specific IgE and the second of anaphylaxis to CMC associated with a barium suspension in contact with GI tract mucosa. CMC as an excipient in medicinal products may therefore be a risk factor for severe anaphylaxis after injection or following contact with GI tract mucosa. Sensitization and allergic reactions by CMC in food additives have to be considered.

PMID: 20128230 [PubMed - indexed for MEDLINE]