Safety Assessment of Magnesium Sulfate as Used in Cosmetics

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

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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Memorandum

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

A tentative report with a conclusion stating that magnesium 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 Magnesium 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 (pcpc1 pdf file).

Study summaries on the skin irritation and sensitization potential of magnesium sulfate in mice, available at the European Chemicals Agency's (ECHA) website, have been added to the 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; however, details relating to the test protocol (number of animals, etc.) were not included. The Panel needs to determine whether results from the skin irritation test warrant deletion of the "safe when formulated to be non-irritating" qualification from the tentative conclusion and revision of the report discussion accordingly.

Ultimately, after reviewing the available data, the Panel needs to determine whether a final report with a revised conclusion should be issued at this Panel meeting.

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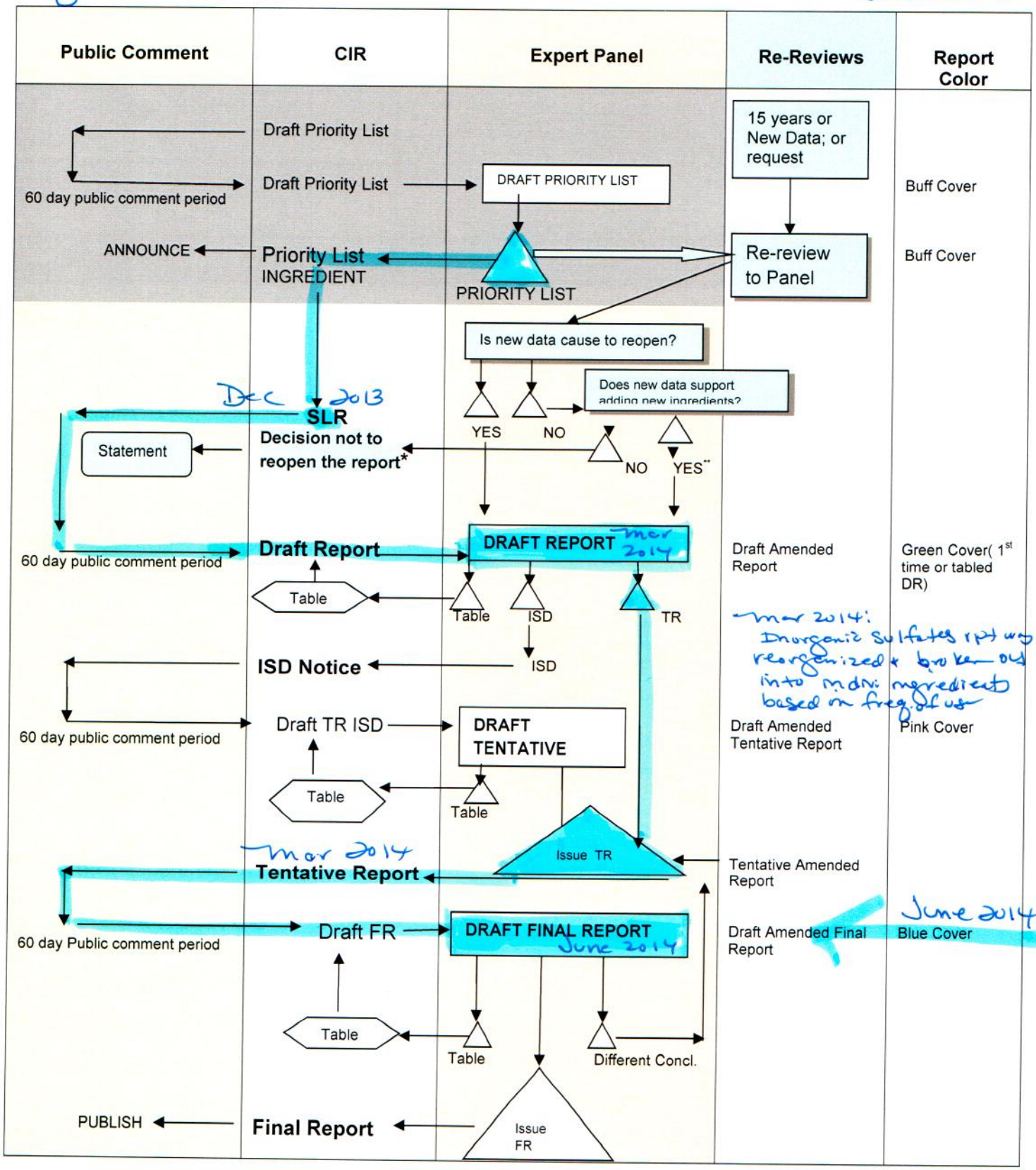
SAFETY ASSESSMENT FLOW CHART

Magnesium Sulfate

June 2014



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

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

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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.

It was noted noted that the history of safe medical use of magnesium 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 magnesium 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 magnesium sulfate should be formulated to be non-irritating.

The Panel issued a tentative safety assessment for public comment with the conclusion that magnesium 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.

Study summaries on the skin irritation and sensitization potential of magnesium sulfate in mice, available at the European Chemicals Agency's (ECHA) website, have been added to the safety assessment.

Magnesium Sulfate
Check List for June, 2014. Analyst – Wilbur Johnson

			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Magnesium Sulfate			X		X				X		X		X		X	X	X	X	X	

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

PubMed Searches

Search Terms

Magnesium Sulfate
CAS No. 18939-43-0
CAS No. 7487-88-9

Literature Search Updates

4/24/2014

Day 1 of the March 17-18, 2014 CIR Expert Panel Meeting – Dr. Belsito's Team

Magnesium 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. LIEBLER: So aluminum sulfate's got 29 uses. Magnesium sulfate's got 23. Calcium sulfate's got 26.

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. LIEBLER: Okay, 510 for magnesium sulfate. Sorry, Wilbur. I made a note.

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

depth.

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.

Day 1 of the March 17 -18, 2014 CIR Expert Panel Meeting – Dr. Marks' Team

Magnesium 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 HRIPT 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 HRIPT 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

capture that in the -- Wilbur?

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 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

Magnesium 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 Magnesium Sulfate as Used in Cosmetics

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

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT: Magnesium Sulfate functions as a bulking agent in cosmetic products, and is being used at concentrations up to 11% and 25% in leave-on and rinse-off products, respectively. The CIR Expert Panel noted that the history of safe medical use of magnesium sulfate indicates no significant toxicity concerns relating to systemic exposure to these ingredients. Furthermore, the extensive clinical experience of the Panel, including the results of numerous patch tests, indicates that magnesium 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 magnesium sulfate should be formulated to be non-irritating. The Panel concluded that magnesium sulfate is safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating.

INTRODUCTION

The safety of magnesium sulfate, an inorganic sulfate, as used in cosmetics is reviewed in this safety assessment. Magnesium sulfate functions as a bulking agent in cosmetic products.

CHEMISTRY

Definition and Structure

Magnesium sulfate (CAS Nos. 18939-43-0 and 7487-88-9) is the inorganic salt that conforms to the formula that is included in Figure 2 below.[2] It is the magnesium salt of sulfuric acid.

$$MgSO_4$$

Figure 2. Formula for Magnesium Sulfate

Physical and Chemical Properties

Magnesium sulfate, available in the form of efflorescent crystals, has a molecular weight of 120.37, and is soluble in water and sparingly soluble in alcohol.[3]

Method of Manufacture

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.[1] 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. For example, hydrated magnesium sulfate can be mined as kieserite or epsomite (Epsom salts), or it can be prepared by dissolving magnesium oxide, magnesium hydroxide, or magnesium carbonate in sulfuric acid. Heating of this hydrate reversibly drives off water and produces anhydrous magnesium sulfate (a potent desiccant).

USE

Cosmetic

Magnesium sulfate functions as a bulking agent in cosmetic products.[4]

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), magnesium sulfate is being used in a number of rinse-off an leave-on cosmetic products.[5] 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 25% (in paste masks - rinse-off products) and 11% (in hair sprays - leave-on products).[6] Summarized data on the frequency and concentration of use of magnesium sulfate in cosmetic products are presented in Table 1.

Cosmetic products containing magnesium sulfate may be applied to the skin and hair, 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.

Magnesium sulfate is being used at concentrations up to 11% and 1% in cosmetic products that are sprayed (hair and foot sprays, respectively) and at concentrations up to 1% in powders (foot 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.[7,8,9,10] 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.[7,8]

Non-Cosmetic

Magnesium sulfate is an FDA-approved direct food additive that is generally recognized as safe.[12] Additionally, FDA has stated that magnesium sulfate heptahydrate should be listed on the label of a drug product as Epsom salt, which may be used as a laxative.[15] According to other sources, magnesium sulfate is an anticonvulsant that is used to prevent or treat seizures in obstetric patients with preeclampsia or eclampsia, and as a tocolytic agent in patients with premature labor.[13,14] It is also used to prevent early mortality in patients with acute myocardial infarction and, in asthmatic patients, as an adjunctive treatment for acute exacerbations of moderate to severe asthma.

TOXICOKINETICS

Animal

Groups of pregnant female Long-Evans rats were injected s.c. with magnesium sulfate according to the following procedure: One group received a single 270 mg/kg s.c. injection of magnesium sulfate. Two other groups received a 270 mg/kg loading dose of magnesium sulfate s.c., followed by 27 mg/kg every 20 minutes for 2 h or 4 h. The gestation days on which dosing occurred were not stated. Magnesium crossed the placenta, entered the fetal blood-brain barrier, and was concentrated in the forebrain.[16]

Human

The concentration in serum and the cumulative renal excretions of magnesium were measured in 3 eclamptic and 7 severely eclamptic patients given an initial therapeutic dose of magnesium sulfate i.v. (3 g) and intramuscularly (10 g).[17] The highest single plasma level was 6.0 mEq per liter (7.2 mg/100 ml) at 60 minutes post-treatment in an oliguric eclamptic woman. The average peak level at 60 minutes was 4.5 mEq. per liter. At the end of 4 h, the cumulative renal excretions ranged from 38% to 53% of the injected dose.

Magnesium sulfate (U.S.P., 13.9 g) was administered orally to 7 healthy men (ages not stated) in 4 equal hourly increments.[18] Urinary excretion (corrected for baseline excretion rate) was described as an amount of inorganic sulfate equivalent to 30.2 ± 17.2% of the administered dose during the first 24 h. Excretion during the subsequent 48 h was negligible.

TOXICOLOGY

Acute Toxicity

Dermal

Anhydrous magnesium sulfate (50%) was applied to the ears of mice (number not stated) in a preliminary skin irritation study, performed prior to the sensitization study.[19] The results for these studies appear later in the report text. All auricular lymph nodes in test and control aninmals were considered normal in size. Body weights and body weight gain

reported for test animals remained in the same range when compared to controls. The slight body weight loss reported for some animals was not considered toxicologically significant. There were no symptoms of systemic toxicity, and none of the animals died.

Intravenous

Magnesium sulfate was administered i.v. to groups of Crj:CD(SD) rats (males and females, 6 weeks old) at doses of 90, 130, 200, 300, and 450 mg/kg.[20] Deaths occurred at doses ≥ 200 mg/kg, and the LD_{50} values were 206 mg/kg and 174 mg/kg for males and females, respectively. Tonic convulsions, abnormal gait, and tachypnea were observed in surviving animals dosed with ≥130 mg/kg. These signs were transient and the animals had returned to normal by 15 minutes post-dosing. There were no treatment-related changes in body weight or gross pathology in any dose group. In a second experiment, magnesium sulfate was infused into groups of female Beagle dogs (6 months old) at doses of 75, 300, and 1,200 mg/kg (12.5, 50, and 200 mg/kg/h) for 6 h. Deaths were not observed in any of the dose groups. The following signs were observed in the 1,200 mg/kg dose group: vomiting, decreased spontaneous movement, staggering gait, prone position, and flush of the conjunctiva and ear auricles. These signs were transient and the animals had returned to normal by 1 h post-dosing. There were no treatment-related changes in body weight, food consumption, or gross pathology.

Repeated Dose Toxicity

Inhalation

Male Wistar rats were exposed (inhalation exposure) to 2 types of magnesium sulfate whiskers 5 days per week (6 h/day) for 4 weeks or for 1 year.[21] Results from the 1-year study are included in the Carcinogenicity section. Magnesium sulfate whisker is a manmade mineral fiber that is synthesized from magnesium sulfate and magnesium hydroxide by hydrothermal reaction at 100˚C to 300˚C. In the 4-week study, short whisker (mean diameter = 1.5 µm) was tested at a mean concentration of 2.3 mg/m^3 and long whisker (mean diameter = 1.8 µm) was tested at a mean concentration of 4.0 mg/m^3. The 124 rats in the 4-week experiment were divided into 3 groups (42, 42, and 40 rats per group for short whiskers, long whiskers, and controls, respectively). Five or six rats in each group were killed and dissected. Few whiskers were detected in rat lungs, even at day 1 post-exposure. This finding suggested that magnesium sulfate whiskers are dissolved and eliminated rapidly from the lungs. There was no indication that adverse effects were observed in this study.

Intravenous

In a 2-week study, groups of female Beagle dogs received the following i.v. doses of magnesium sulfate: 12.56, 50, 100, and 200 mg/kg/h.[22] The test substance was administered as 24-h i.v. infusions. Dosing was followed by a 2-week observation period. One animal in the 200 mg/kg/h dose group died at 32 h, and another animal was euthanized because of morbidity at the same time. Treatment-related changes in the 100 mg/kg/h dose group were as follows: decreased food consumption and body weight gain, anemia, mild prolongation of conduction time in the electrocardiogram, and tubular basophilia in the kidneys. Additionally, decreased calcium level was reported for animals that received doses ≥ 50 mg/kg/h, and was considered toxicologically insignificant. These treatment-related changes were not observed at the end of dosing. The NOAEL was considered to be 50 mg/kg/h (for 24 h) in this study.

Magnesium sulfate was administered (24-h i.v. infusion) to groups of 3 female Beagle dogs at doses of 12.5, 50, and 100 mg/kg/h for 2 weeks.[23] Dosing was followed by a 2-week observation period. None of the animals died. The following treatment-related changes were reported (highest dose group): decreased feed consumption and body weight gain, anemic changes, increased urine volume, decreased serum calcium level, increased inorganic phosphorus level, slight prolongation of conduction time in the electrocardiogram, and tubular basophilia in the kidneys. The NOAEL was considered to be ≤ 50 mg/kg/h (for 24 h) in this study.

Skin Irritation

A preliminary skin irritation study (mice) was performed prior to the skin sensitization study summarized below.[19] The test procedure was not included. Skin irritation of the ears was not observed in any of the animals tested with 50% anhydrous magnesium sulfate. Additionally, there was no evidence of macroscopic abnormalities of the surrounding area.

Skin Sensitization

The skin sensitization potential of anhydrous magnesium sulfate was evaluated using the mouse local lymph node assay, according OECD Guideline 429.[19] Three groups of 5 mice were used, and the dorsal surface of both ears was epidermally treated with the test substance (10%, 25%, and 50%) at a dose volume of 25 µL/ear. A vehicle control group was also included in the study. The animals were then injected i.v. with ^{3}H-methyl thymidine, killed, and the draining auricular lymph node of each ear was excised. Lymph nodes were pooled for each animal, and cell suspensions prepared. The stimulation index (SI) was calculated for each group. The SI is defined as the ratio of the DPM/group compared to the DPM/vehicle control group. Because there was no indication that the test substance elicited an SI of ≥ 3 when tested jup to a concentration of 50%, anhydrous magnesium sulfate was considered a non-sensitizer.

Case Reports

Two patients (29 ad 32 years old) were treated i.v. with magnesium sulfate for preterm labor.[24] Both patients were started with a 4 mg i.v. loading dose of magnesium sulfate. An urticarial reaction, rapid and sudden onset, was observed in both patients, and the eruption cleared when dosing with magnesium sulfate was discontinued.

A 29-year-old female presented with generalized tonic-clonic seizure at 17 h post-partum.[25] Infusion with magnesium sulfate involved a loading dose of 4 g (16 mmol) by burette, and the patient received 100 mmol over approximately 20 minutes. A peak serum magnesium level of 6.87mmol/l was reported. The absence of circulatory compromise or arrhythmias was noted. [26]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Animal

The following doses of magnesium sulfate were administered to Crj:CD(SD) female rats s.c. three times per day on days 15 through 20 of gestation: 250, 500, and 1,000 mg/kg.[27] The control group and 250 mg/kg group each consisted of 19 rats. The remaining 2 dose groups each contained 20 rats. Effects of the test material on the dams and F_1 animals were examined. Dams dosed with 500 and 1,000 mg/kg had decreased food consumption, Hypolocomotion, pronation, bradypnea, and decreased body weight gain were observed in the 1,000 mg/kg dose group. There were no test material-related effects on delivery or lactation, and necropsy results were normal. Results for F_1 animals dosed with 1,000 mg/kg were as follows: low body weight, delays in differentiation (eruption of lower incisor and opening of eyelid), and reversible changes in ribs (wavy ribs). However, there were no test material-related effects on viability, functional examinations, behavioral tests, or reproductive ability. It was concluded that the NOAEL for general toxicological effects on the dams was 250 mg/kg/day (3 times per day), and that the NOAEL for reproductive ability and development were 1,000 mg/kg/day (3 times per day) and 500 mg/kg/day (3 times per day), respectively.

Human

Over a period of 14 years, 7,000 infants were born to mothers who had received magnesium sulfate parenterally because of preeclampsia or eclampsia.[28] A 50% magnesium sulfate ($MgSO_4 \cdot 7H_2O$, USP) solution was injected intramuscularly (30 to 40 g doses, during 24 h) into the gravida. This regimen was continued as long as the mother had demonstrable knee jerks, urine output of at least 100 ml during 4 h, and no depression of respiration. The serum level of magnesium in the fetus rapidly approached the maternal level, but could not be correlated with any adverse effect. Dosing did not have any observable deleterious effects on the fetus or newborn.

Five neonates were born to mothers who had been treated i.v. with magnesium sulfate for tocolysis.[29] The neonates were retrospectively reviewed to assess the presence of radiographic, clinical, and biochemical abnormalities. Two infants had radiographic bony abnormalities; one had frank rachitic changes and dental enamel hypoplasia. One of these patients as well as an additional infant had transient hypocalcemia. It was hypothetized that prolonged infusion of magnesium sulfate, especially when initiated during the second trimester, may lead to fetal parathyroid gland suppression, with consequent abnormalities resembling rickets.

The effects of maternal magnesium sulfate treatment on newborns were studied.[30] The subjects in this study were newborn infants, delivered at ≥ 34 weeks of gestation, whose mothers had received a minimum of 12 h of i.v. magnesium sulfate therapy prior to delivery. A total of 26 magnesium-exposed and 26 control infants was enrolled. The mean dose of

magnesium sulfate prior to delivery was 51.2 ± 24 g, and the mean duration of therapy was 23.1 ± 120 h. The mean maternal serum magnesium level before delivery was 5.8 ± 1.1 mg/dl. Infants exposed to magnesium sulfate in utero had a higher incidence of hypotonia and lower median Apgar scores, compared to control infants ($p < 0.001$). However, there was no association between adverse outcomes and maternal serum magnesium concentrations at the time of delivery, duration of treatment, or dose of magnesium sulfate. Pneumocardiogram data were similar between magnesium sulfate-exposed and control infants (all, $p \geq 0.16$).

In a controlled trial, mothers in preterm labor were randomized as follows: magnesium sulfate tocolysis (46 mothers, 55 newborns) and saline control (28 mothers, 29 newborns).[31] Magnesium sulfate was administered as a 4-g bolus, followed by infusion of 2 to 3 g of magnesium sulfate per hour. Children with adverse outcomes had higher umbilical cord magnesium levels at the time of delivery. In regression models that controlled for confounders, which included very low birth weight, magnesium remained a significant risk factor (adjusted odds ratio = 3.7; 95% CI of 1.1 to 11.9; P = 0.03). Dosing with magnesium sulfate was associated with 11 composite adverse pediatric outcomes, which included intraventricular hemorrhage (IVH) and periventricular leucomalacia (PVL), and cerebral palsy. However, the differences in this trial were not statistically significant (magnesium sulfate: 37% [11 adverse events in 30 infants]; saline solution: 21% [6 adverse events in 29 infants] (P = 0.25).

Between January 2000 and February 2009, 6,654 women with preeclampsia were treated with an intravenous infusion of magnesium sulfate, with the goal of achieving a therapeutic range of 4 to 7 mE/L (2.0 to 3.5 mmol/L).[32] Eighty-eight infants (6% of the infants) were diagnosed with hypotonia. Lowder 1-minute and 5-minute Apgar scores, intubation in the delivery room, admission to special care nursery, and hypotonia were all significantly increased as maternal serum magnesium concentrations increased prior to birth.

GENOTOXICITY

Bacterial Cells

Magnesium sulfate was evaluated for genotoxicity in the Ames test using the following *Salmonella typhimurium* strains: TA92, TA94, TA98, TA100, TA1535, and TA1537.[33] The test substance (in phosphate buffer) was evaluated at doses up to 100 mg/plate with metabolic activation, and results were negative in all bacterial strains tested. In another Ames test, magnesium sulfate was evaluated in the following bacterial strains at doses up to 5,000 µg/plate, with and without metabolic activation: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A.[34] Magnesium sulfate did not induce an increase in the incidence of reverse mutations in any of the bacterial strains tested in this assay.

The genotoxicity of magnesium sulfate was evaluated in the SOS Chromotest using *Escherichia coli* strain PQ37, with and without metabolic activation.[35] The SOS Chromotest is a colorimetric assay that measures the expression of genes induced by genotoxic agents in *E. coli* by means of fusion with the structural gene for β-galactosidase. Magnesium sulfate ($MgSO_4$,$7H_2O$) was tested at concentrations up to 30,000 nM/ml and was not genotoxic, with or without metabolic activation.

Mammalian Cells

In a chromosome aberrations assay using Chinese hamster ovary cells,[36] the genotoxicity of magnesium sulfate (dissolved in physiological saline) was evaluated at concentrations up to 4 mg/ml in culture. Magnesium sulfate did not induce chromosomal aberrations in this assay.[33] In another chromosomal aberrations assay, a Chinese hamster lung fibroblast cell line (CHL/IU) was used (direct and metabolic activation methods), and magnesium sulfate was evaluated at concentrations up to 5.0 mg/ml, with and without metabolic activation.[34] Magnesium sulfate did not induce an increase in the incidence of chromosomal aberrations or genome mutation (polyploidy) in this assay.

The frequency of sister chromatid exchanges (SCEs) in cultures of human peripheral blood lymphocytes (from single donor) incubated with magnesium sulfate was evaluated.[37] Cultures containing the following concentrations of magnesium were incubated for 96 h: 62.5 µg/ml, 125 µg/ml, 250 µg/ml, 500 µg/ml, and 1,000 µg/ml. At each experimental point and in the corresponding control (unspecified), 40 metaphases of the second mitosis were analyzed. At all concentrations tested, the frequency of SCEs in cultures incubated with magnesium sulfate did not differ significantly ($P > 0.05$) from that of the control (6.20 ± 0.43 µg/ml). It was concluded that magnesium sulfate was not genotoxic.

Antigenotoxicity

The effect of magnesium sulfate on metal-induced mutagenicity was evaluated in the Ames test using *Salmonella typhimurium* strain TA97.[38] The preincubation mutagenicity test was performed in triplicate by adding the following, in that order, to tubes incubated for 30 minutes: 500 µl buffer or ddH_20, freshly prepared metal dilutions (50 µl), bacterial cell culture (100 µl), and $MgSO_4$ (50 µl). One of the following metals was included in one of the tubes (final volume = 700 µl), which was incubated for 30 minutes: Co^{++} (up to 800 µM), Fe^{++} (up to 1,000 µM), Mn^{++} (up to 1,200 µM), Zn^{++} (up to 1,000 µM), and Cd^{++} (up to 200 µM). Magnesium sulfate inhibited the mutagenicity of Fe^{++}, Mn^{++}, and Zn^{++}, had only a slight effect on the mutagenicity of Co^{++}, and had no effect on the mutagenicity of Cd^{++}.

CARCINOGENICITY

A magnesium sulfate man-made fiber (diameter = 0.45 µm; length = 22.4 µm) was administered intratracheally to a group of 20 hamsters.[39] Intratracheal administration involved a dose of 2 mg per animal weekly for 5 weeks (total of 10 mg/animal). Tumors were observed in 9 of 20 hamsters dosed with magnesium sulfate, but were not observed in the control group. The primary sites of the tumors were not only in the pleural cavity, but also in the intracelial organs, kidney, adrenal gland, bladder, and uterus. Only a few tumors were identified as mesotheliomas at histological examination. The following changes were observed in the lungs: fibrosis, pleural thickening, and chronic inflammatory changes. However, these changes appeared to have been too mild to promote the development of pneumoconiosis.

The tumorigenicity of magnesium sulfate fibers was evaluated using 20 female Syrian hamsters (ages not stated).[40] Each 500 mg of fiber was suspended in 50 ml of sterilized saline with 0.25 g of sodium carboxymethylcellulose to delay fiber sedimentation. The magnesium sulfate fiber suspension was sonicated and then injected intratracheally (0.2 ml/animal) once per week for 5 weeks. Vehicle alone was administered to 20 control hamsters according to the same procedure. At 2 years post-administration, the animals were killed and necropsy performed. Due to solubility, magnesium sulfate fibers could not be detected in the lung tissue of hamsters at 2 years post-administration. There were 9 tumor-bearing animals in the group dosed with magnesium sulfate fibers, and the tumors were defined as follows: adrenal gland (a neuroblastoma, a cortical adenoma, and A & B cell tumor), pleural mesothelioma (2 epithelial types), kidney (a malignant histocytoma and an anaplastic tumor), lung (1 tumor, unspecified cell type), uterus (1 leiomyosarcoma), and bladder (1 leiomyoma). Malignant histocytoma of the kidney and leiomyosarcoma of the uterus were observed in the same hamster. Tumors were not observed in vehicle control hamsters.

Wistar rats were exposed (inhalation exposure) to long and short magnesium sulfate whisker 5 days per week (6 h/day) for 1 year.[21] Long and short whiskers were defined as those having a mean diameter of 1.8 µm and 1.5 µm, respectively. The exposure groups were defined as follows: long whisker (27 rats), short whisker (27 rats), and controls (26 rats). Long and short whiskers were tested at mean concentrations of 4.0 mg/m^3 and 2.3 mg/m^3, respectively. Few whiskers were detected in rat lungs, even at day 1 post-exposure. This finding suggested that magnesium sulfate whiskers are dissolved and eliminated rapidly from the lungs. Histopathological examination indicated that the lung tumor incidence was not significantly different from that of control rats.

SUMMARY

Magnesium sulfate functions as a bulking 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), magnesium sulfate is being used in a number of rinse-off and leave-on cosmetic 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 25% (in paste masks - rinse-off products) and 11% (in hair sprays - leave-on products).

Hydrated magnesium sulfate can be prepared by dissolving magnesium oxide, magnesium hydroxide, or magnesium carbonate in sulfuric acid. Heating of this hydrate reversibly drives off water and produces anhydrous magnesium sulfate.

Magnesium sulfate crossed the placenta and entered the fetal brain and other tissues, following s.c. injection into pregnant rats. In eclamptic patients dosed i.v. or intramuscularly with magnesium sulfate, cumulative renal excretions ranged from 38% to 53% of the injected dose at the end of 4h. Urinary excretion of inorganic sulfate (30.2 ± 17.2% of administered dose) was noted in healthy male subjects during the first 24h after oral dosing with magnesium sulfate. Excretion during the next 48h was negligible.

Anhydrous magnesium sulfate (50%) did not induce systemic toxicity when applied to the skin of mice.

Magnesium sulfate was administered i.v. to groups of Crj:CD(SD) rats at doses up to 450 mg/kg, and the LD_{50} values were 206 mg/kg and 174 mg/kg for males and females, respectively. In a second experiment, magnesium sulfate was infused into groups of female Beagle dogs at doses up to 1,200 mg/kg for 6 h. Deaths were not observed in any of the dose groups.

Male Wistar rats inhaled 2 types of magnesium sulfate whiskers 5 days per week (6 h/day) for 4 weeks. Short whisker (mean diameter = 1.5 µm) was tested at a mean concentration of 2.3 mg/m^3 and long whisker (mean diameter = 1.8 µm) was tested at a mean concentration of 4.0 mg/m^3. Few whiskers were detected in rat lungs, even at day 1 post-exposure, and this finding suggested that magnesium sulfate whiskers are dissolved and eliminated rapidly from the lungs. There was no indication that adverse effects were observed.

Female Beagle dogs received 24-h i.v. infusions of magnesium sulfate at doses up to 200 mg/kg/h. An NOAEL of 50 mg/kg/h was reported. In another similar study, an NOAEL of $\leq$ 50 mg/kg/h was reported for female Beagle dogs infused with magnesium sulfate at doses up to 100 mg/kg/h for 2 weeks.

Anhydrous magnesium sulfate (50%) did not induce skin irritation in mice, and was classified as a non-sensitizer in the mouse local lymph node assay.

An urticarial reaction was observed in 2 patients who were treated i.v. with magnesium sulfate (4 mg) for preterm labor. There was no evidence of circulatory compromise or arrhythmias in a female patient with generalized tonic-clonic seizure post-partum who was subsequently infused with magnesium sulfate (100 mmol over ~ 20 minutes).

In a reproductive and developmental toxicity study, groups of pregnant female rats received doses up to 1,000 mg/kg s.c. 3 times per day on gestation days 15 through 20. The NOAEL for general toxicological effects on the dams was 250 mg/kg/day, and the NOAELs for reproductive and developmental toxicity were 1,000 mg/kg/day and 500 mg/kg/day, respectively. Results were mixed regarding adverse outcomes in the infants of mothers dosed with magnesium sulfate during pregnancy.

Magnesium sulfate was not genotoxic in *in vitro* assays involving bacterial and mammalian cells.

Following intratracheal administration of magnesium sulfate man-made fiber (diameter = 0.45 µm; length = 22.4 µm) to 20 hamsters at a dose of 2 mg weekly for 5 weeks, tumors were observed in 9 hamsters. The primary sites of the tumors were the pleural cavity, intracelial organs, kidney, adrenal gland, bladder, and uterus. In another study, the tumorigenicity of magnesium sulfate was also evaluated using 20 hamsters. Each 500-mg fiber was suspended in sterilized saline and sodium carboxymethylcellullose and injected intratracheally (0.2 ml per animal). Again, tumors were observed in basically the same organs of 9 hamsters.

Groups of 27 Wistar rats were exposed (inhalation exposure) to long and short magnesium sulfate whisker 5 days per week (6 h/day) for 1 year. Long and short whiskers had mean diameters of 1.8 µm and 1.5 µm, respectively. These materials were tested at mean concentrations of 4.0 mg/m^3 (long whisker) and 2.3 mg/m^3 (short whisker), respectively. Histopathological examination indicated that the lung tumor incidence was not significantly different from that of control rats.

DISCUSSION

The Panel noted that the history of safe medical use of magnesium sulfate indicates no significant toxicity concerns relating to systemic exposure to these ingredients. Furthermore, the extensive clinical experience of the Panel, including the results of numerous patch tests, indicates that magnesium 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 magnesium sulfate should be formulated to be non-irritating. Magnesium sulfate is used in leave-on products (hair sprays) at concentrations up to 11%.

Magnesium sulfate is being used at concentrations up to 11% in cosmetic products that are sprayed (hair and foot sprays) and at concentrations up to 1% in powders (foot 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, repeated dose (inhalation) toxicity, reproductive

and developmental toxicity, and carcinogenicity. 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.

CONCLUSION

The CIR Expert Panel concluded that magnesium 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 Magnesium Sulfate.[5,6]

	# of Uses	Conc. (%)
Totals/Conc. Range	504	0.00001-49
Duration of Use		
Leave-On	317	0.002-11
Rinse off	54	0.00001-25
Diluted for (bath) Use	34	0.1-49
Exposure Type		
Eye Area	22	0.4-2.1
Incidental Ingestion	5	NR
Incidental Inhalation-Sprays	116	0.5-11
Incidental Inhalation -Powders	96	1
Dermal Contact	365	0.00001-49
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	65	0.01-15
Hair-Coloring	NR	NR
Nail	1	NR
Mucous Membrane	49	0.00001-49
Baby Products	NR	0.7

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.

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2014 FDA VCRP Data

Magnesium Sulfate

02A - Bath Oils, Tablets, and Salts	31
02B - Bubble Baths	2
02D - Other Bath Preparations	1
03C - Eye Shadow	3
03D - Eye Lotion	6
03G - Other Eye Makeup Preparations	13
05A - Hair Conditioner	19
05F - Shampoos (non-coloring)	7
05G - Tonics, Dressings, and Other Hair Grooming Aids	17
05H - Wave Sets	1
05I - Other Hair Preparations	21
07A - Blushers (all types)	1
07B - Face Powders	1
07C - Foundations	73
07D - Leg and Body Paints	1
07E - Lipstick	5
07F - Makeup Bases	10
07H - Makeup Fixatives	1
07I - Other Makeup Preparations	25
08G - Other Manicuring Preparations	1
10A - Bath Soaps and Detergents	9
10E - Other Personal Cleanliness Products	1
11A - Aftershave Lotion	6
11E - Shaving Cream	1
12A - Cleansing	8
12C - Face and Neck (exc shave)	33
12D - Body and Hand (exc shave)	16
12E - Foot Powders and Sprays	1
12F - Moisturizing	32
12G - Night	12
12H - Paste Masks (mud packs)	8
12I - Skin Fresheners	1
12J - Other Skin Care Preps	34
13A - Suntan Gels, Creams, and Liquids	3
13B - Indoor Tanning Preparations	1
Total	**405**

Personal Care Products Council
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Memorandum

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

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

DATE: April 17, 2014

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

Key Issues

Information on Magnesium Sulfate submitted to ECHA still needs to be added to this report.

The Introduction to this report should note that magnesium is essential, and refer the reader to a reference such as the NIH fact sheet on magnesium http://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/ for additional details about how it is used by the body.

p.2 - The only OTC use for which Magnesium Sulfate is approved is as a laxative. 21CFR310.545 is for substances for which there "are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses."

Additional Comments

p.1 - Please add the CAS numbers for Magnesium 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 and one formula (for Magnesium Sulfate) is sufficient.

p.2, 6 - 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, 6, 7 - 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., 25% in paste masks and mud packs and 11% in hair spray products.

p.2 - The 11% concentration was associated with two hair products, not a foot product. It should state that the form of the product (1% Magnesium Sulfate) in the foot powder and spray category is not known (it could be a spray, it could be a powder, or it could be a another form).

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p.2 - In the Non-Cosmetic Use section, it should also be noted that Magnesium Sulfate is a GRAS direct food substance (see 21CFR184.1443).

p.5 - All of the studies summarized in the Genotoxicity section are *in vitro* studies. The studies presented under the *in vitro* subheading are bacterial studies, while the studies under the *in vivo* subheading are *in vitro* studies conducted in mammalian cells.

p.5 - Please check the units used in reference 32. As nM means nanomole/L, the meaning of nM/ml is not clear.

p.6 - In the third paragraph of the Summary, please delete "and manganese sulfate" as manganese sulfate is no longer a subject of this report.

p.7 - As all the genotoxicity studies were *in vitro*, the following sentence in the Summary needs to be revised: "Magnesium Sulfate was not genotoxic in *in vitro* or *in vivo* assays." It should state that Magnesium Sulfate was not genotoxic in *in vitro* assays in bacterial and mammalian cells.