Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review

Release Date: May 13, 2016

Panel Meeting Date: June 6-7, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst.

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*On the in-text Table references use “Ctrl + left click” in Word, or double (left) click in the PDF version, to link directly to the corresponding Table at the end of the document.
Memorandum

To: CIR Expert Panel Members and Liaisons
From: Laura N. Scott
Senior Scientific Writer
Date: May 13, 2016
Subject: Draft Final Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics

At the March 31-April 1, 2016 CIR Expert Panel meeting, the Panel voted in favor of reopening the Final Report on the Safety Assessment of Sodium Sulfate that was issued in 2000. This decision was based on the 2016 VCRP data reciting a significant increase in frequency of use (777 up from 28 uses originally) and the 2015-2016 Council industry survey showing an increase of use concentration in leave-on cosmetic products (2% in hair tonics and other grooming aids). This exceeds the concentration for leave-on products recited in the original report, in which the Panel concluded that Sodium Sulfate is safe as used in rinse-off cosmetic formulations and safe for use up to concentrations of 1% in leave-on formulations (original assessment identified as SODSUL062016prev). A Tentative Amended Report for public comment was issued at the March 2016 meeting with the conclusion: safe as used in cosmetics when formulated to be non-irritating.

Enclosed is the Draft Final Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics (identified as SODSUL062016rep in the pdf document). Additionally, the CIR report history (SODSUL062016hist), Literature search strategy (SODSUL062016strat), Ingredient Data profile (SODSUL062016prof), Process flow chart (SODSUL062016flow), 2016 FDA VCRP data (SODSUL062016FDA), Minutes from the original review of Sodium Sulfate, and Minutes from the March 2016 Panel Meeting (SODSUL062016min) are included for the Panel’s review.

The following were added to this Draft Final Amended Report:

1. The use of Sodium Sulfate as an inactive ingredient in FDA approved drug products at the following concentrations: up to 1.2% (ophthalmic exposure), up to 0.03% (inhalation exposure), up to 182 mg (oral exposure), up to 1.14% (iv infusion exposure) were added to Non-Cosmetic Use and mentioned in the Summary and Discussion.
2. 3-month, repeated-dose dermal exposure toxicity data (dermal exposure of Sodium Sulfate 16%, w/w; dermal irritation data from this study was seen by the Panel in the report at the March 2016 Meeting) were added to the Toxicological Studies section under Subchronic Toxicity and captured in the Summary.
3. A few summary sentences of inhalation data (human subjects) from the original report were added to the Toxicological Studies-Acute Toxicity, Clinical Studies-Occupational Exposure, and Discussion.
4. A few summary sentences of development/reproduction data from original report were added to DART Studies.
5. A small paragraph on sulfate metabolism was added to the Toxicokinetic Studies section.
6. Abstract, Discussion, and Conclusion sections were added.

Council comments on the Amended Safety Assessment (SODSUL062016pcpc_1) and on the Tentative Amended Safety Assessment (SODSUL062016pcpc_2) were received and have been addressed.

[Note: In the Draft Final Amended Report the in-text Table references are linked directly to the corresponding Table at the end of the document. In the Word version use “Ctrl + left click” on the in-text link and in the PDF version simply double (left) click on the in-text link to go directly to the Table.]

After reviewing the Draft Final Amended Report, the Panel will need to identify any modifications that need to be made and consider issuing a Final Amended Report.
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY: Sodium Sulfate

MEETING: June 2016

Public Comment  CIR  Expert Panel  Re-Review  Rpt Status

- 60 day public comment period
- IDA Notice
- Draft TAR
- Tentative Amended Report April 12, 2016
- 60 day Public comment period
- Draft FAR
- Final Amended Report

- announce
- 15 years since last review
- PRIORITY LIST
- New Data; or request
- Re-review to Panel Mar 2016

- Are new data cause to reopen?
- YES
- DRAFT AMENDED REPORT*
- No
- DRAFT TENTATIVE AMENDED REPORT
- IDA Notice
- Draft TAR
- Tentative Amended Report April 12, 2016
- 60 day Public comment period
- Draft FAR
- Final Amended Report

- Are new ingredients appropriate for inclusion/re-open?
- Yes
- DRAFT FINAL AMENDED REPORT June 2016
- Issue TAR
- Table
- Different Conclusion

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

**June 1996**-Insufficient Data Announcement issued; Concentration of use and Human skin irritation study at concentration of use were requested

**December 1996**-The Panel unanimously agreed to issue a Tentative Report with the conclusion that Sodium Sulfate is safe at concentrations up to 1.0% in leave-on products and safe as used in rinse-off products. This conclusion was based on negative results in the sensitization study included in the Draft Report.

**June 1997**-The Panel voted unanimously in favor of issuing a Final Report with the conclusion that Sodium Sulfate is safe as used in rinse-off formulations, and safe up to 1% in leave-on formulations.

**2000**-Panel concluded that Sodium Sulfate (both anhydrous and decahydrate forms) is safe as used in rinse-off formulations, and safe up to 1% in leave-on formulations.

**April 1, 2016**-The Panel voted unanimously in favor of re-opening the Final Report on the Safety Assessment of Sodium Sulfate from 2000, based on increased frequency of use (777 uses up from 28 originally) and on the increase in use concentration in leave-on products (2% in hair tonics and other grooming aids), which exceeds the “safe up to 1% in leave-on formulations” conclusion from the original report issued in 2000. A Tentative Amended Report for public comment was issued with a conclusion stating that Sodium Sulfate is safe when formulated to be non-irritating.

**April 12, 2016**-The Sodium Sulfate Tentative Amended Report was posted at [www.cir-safety.org](http://www.cir-safety.org) for public comment.

**June 6-7, 2016**-
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Distributed for comment only -- do not cite or quote
Sodium Sulfate Re-Review Search Info

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X-indicates data were available

**PubMed (August 27, 2015):**

CAS #: (7727-73-3) OR 7757-82-6 766 hits/0 useful; ((7727-73-3) AND 7757-82-6) AND “toxicity” 56 hits/0 useful; (sodium sulfate) AND cosmetics 15 hits/0 useful

Email updates are received when new articles (using similar search parameters as above) become available.

**SciFinder (August 27, 2015):**

CAS #: (7727-73-3) from 1995-2015 317 hits/0 useful; “7757-82-6 and toxicity” from 1995-2015 525 hits/0 useful; “7757-82-6 and cosmetics” 1995-2015 25 hits/0 useful

“Keep Me Posted” email updates are received when new articles (using similar search parameters as above) become available.

**ECHA Citations (first link below cited in RR report)**


**TOXNET (not cited in RR)**


PubChem (not cited in RR)

Sodium Sulfate, search date 8/31/15:  https://pubchem.ncbi.nlm.nih.gov/compound/sodium_sulfate#section=Top

ILO-ICSC (not cited in RR)

Sodium Sulfate, search date 9/2/15:  http://www.ilo.org/dyn/icsc/showcard.display?p_card_id=0952

InChem (WHO Series 44 report, not cited in RR)

Sodium Sulfate, searched Google 8/31/15:  http://www.inchem.org/documents/jecfa/jecmono/v44jec07.htm

NICNAS (not cited in RR)


EU Citation (not cited in RR)


SID SIDS Citation (primary source obtained from this link is cited in RR report)


HPVIS/EPA (not cited in RR)

Sodium Sulfate, searched “toxicity and sodium sulfate” 8/31/15:  http://www2.epa.gov/sites/production/files/2015-03/documents/tri_chemical_list_changes_2_27_15.pdf

Technical Data Sheets (not cited in RR)


**FDA’s Inactive Ingredients for Use in Approved Drug Products (cited in RR report)**


**CFR Citations (cited in RR report)**

**21CFR186.1797:** Part 186-Indirect Food Substances Affirmed As Generally Recognized As Safe; Subpart B-Listing of Specific Substances Affirmed as GRAS; Section 186.1797 Sodium sulfate; (a) Sodium sulfate (Na2SO4, Cas Reg. No. 7757-82-6), also known as Glauber’s salt, occurs naturally and exists as colorless crystals or as a fine, white crystalline powder. It is prepared by the neutralization of sulfuric acid with sodium hydroxide. (b) The ingredient is used as a constituent of paper and paperboard used for food packaging, and cotton and cotton fabric used for dry food packaging. (c) The ingredient is used at levels not to exceed good manufacturing practice in accordance with 186.1 (b) (1). (d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

**21CFR177.1200:** Part 177-Indirect Food Additives: Polymers; Subpart B-Substances For Use as Basic Components of Single and Repeated Use Food Contact Surfaces; Section 177.1200 Cellophane; Cellophane may be safely used for packaging food in accordance with the following prescribed conditions: (b) Subject to any limitations prescribed in this part, the optional substances used in the base sheet and coating may include: (4) Substances named in this section and further identified as required. (c) List of substances: Sodium sulfate.

**21CFR172.615:** Part 172-Food Additives Permitted For Direct Addition To Food For Human Consumption; Subpart G-Gums, Chewing Gum Bases and Related Substances; Section 172.615 Chewing gum base; The food additive chewing gum base may be safely used in the manufacture of chewing gum in accordance with the following prescribed conditions: (a) The food additive consists of one or more of the following substances that meet the specifications and limitations prescribed in this paragraph, used in amount not to exceed those required to produce the intended physical or other technical effect. Miscellaneous. Sodium sulfate.
21CFR173.310: Part 173-Secondary Direct Food Additives Permitted In Food For Human Consumption; Subpart D-Specific Usage Additives; Section 173.310 Boiler water additives. Boiler water additives may be safely used in the preparation of steam that will contact food, under the following conditions: (a) The amount of additive is not in excess of that required for its functional purpose, and the amount of steam in contact with food does not exceed that required to produce the intended effect in or on the food. (b) The compounds are prepared from the substances identified in paragraphs (c) and (d) of this section, and are subject to the limitations, if any, prescribed: (c) List of substances: Sodium sulfate.

21CFR73.85: Part 73-Listing of Color Additives Exempt From Certification; Subpart A-Foods; Section 73.85 Caramel. (a) Identity. (2) The food-grade acids, alkalis, and salts listed in this subparagraph may be employed to assist caramelization, in amounts consistent with good manufacturing practice. (iii) Salts: Amonium, sodium, or potassium carbonate, bicarbonate, phosphate (including dibasic phosphate and monobasic phosphate), sulfate, and sulfite.
MINUTES FROM MARCH 2016 PANEL MEETING-SODIUM SULFATE-DR. BELSITO’S TEAM

DR. BELSITO: Okay so sodium sulfate. So this is a rereview of the amended safety assessment of sodium sulfate in 2000. We reviewed that hydrus [anhydrous, spelling correction] and decahydrate forms included safe as used in rinse offs, safe for use in concentration 1 percent in leave on formulations, frequency of uses increased 777 from 28, concentrations of use reported in the original assessment have only increased slightly but there are new categories that have come into play and actually some use of leave on products such as hair tonics have it a 2 percent. We have new data and so based upon this new data do we need to reopen the report and I think we do because we can change our conclusions with restrictions to go safe as used when formulated to be non irritating but I wondered how many other sulfates are out there that could be added to this report and that was not mentioned.

DR. HELDRETH: Our rationale for not proposing the addition came from a report that was proposed two years ago that Wilbur worked on that was a report on sulfate salts. And after much discussion at the panel table we decided that there was a consensus that there is absolutely no good read across or inference between purely inorganic salts. So the grouping the sulfates together was not a good idea and the report broke apart two separate reports on barium sulfate and magnesium sulfate. So when this rereview came up it was not in the forefront of our mind to think of adding new ingredients to this.

DR. KLAAS[EN]: I agree 100 percent.

DR. LIEBLER: Yes.

DR. BELSITO: So basically we're going to reopen to slightly because of the fact of the significant number of new products, significant change in the leave on concentration which would be above what we had previously restricted and the discussion before was really pretty innocent. There were no significant discussion points except for the irritation in the original document is that correct?

MS. SCOTT: Yes.

DR. BELSITO: The document we're seeing is the new one. I'm trying to look at the old one here and really our entire issue was around the 1 percent so I don't think that there was a lot in that. I
mean we'd have to look at the discussion from the original one but I think that was our only real discussion point.

DR. KLAAS[SEN]: There is one thing that I was a little concerned about this but I didn't go back to the literature to look. So there's been a lot of work done on various transporters the last decade and there is a transporter for sulfate and I was wondering if there are any and I don't think this would be a toxicity concern very likely but if there might be people that might have mutations in that transporter and if they might have real problems with sulfate that the normal that's more of an academic interest more than a true toxicity interest. But if there's a nice little story there that one could write about in a paragraph it would make this sound a little bit more scientific of the importance of sulfate. On[e, sp.] of the things that happens with some drugs is that they are sulfated and one of the chemicals that we have the least amount in the body for this process is sulfate. So for example if you take acetaminophen or Tylenol we're all taught that you run out of glutathione is protecting you but way before that you run out of sulfate and so you block that metabolic pathway of a very low dose. So this whole business of sulfate might have a little bit more biological significance then we give it credit for. Maybe we should put a paragraph in there and it might make at least the people that read this realize that we are aware of the importance of sulfate, that it is transported and if you run out of it it can increase the toxicity of other chemicals.

MS. SCOTT: Just so I understand so you're talking about sulfate and not sodium sulfate?

DR. KLAAS[SEN]: Yes.

MS. SCOTT: Okay.

DR. KLAAS[SEN]: That's not going to change the safety here I don't think.

DR. BELSITO: Anything else? Okay. So we're to Apple derived ingredients so at the December meeting we issued a revised tentative report for public comment….

MINUTES FROM MARCH 2016 PANEL MEETING-SODIUM SULFATE-DR. MARKS’ TEAM

DR. MARKS: No, I agree. Any other comments? If not, let's move on to sodium sulfate, and how's the panel doing? Team, how are you doing? Do you need a break around 3:00 or should we move on? You okay? Welcome, Laura.
MS. SCOTT: Thank you.

DR. MARKS: And this is an amended safety assessment of sodium sulfate. It's a re-review in 2000. The panel concluded that sodium sulfate is safe as used in rinse-off formulas and safe for use in concentrations of whatever (inaudible) and leave-on formulations, and I think I'll be seconding a not reopen, but it is being used 2 percent in hair grooming aids, but.

DR. SHANK: Don't reopen.

DR. MARKS: Right, okay. Not reopen. Not reopen. Should we, in the discussion, mention that it's 1 percent is what has been approved, and it's use now 2 percent concentration in some hair grooming aids? No, you don't (inaudible).

MR. BEST: That was my only question. All the concentrations just went up a little above what was authorized, right, including the bath solution.

DR. MARKS: Bath solution -- usually with those they're so diluted that we aren't concerned about when they're highly diluted or when they're (inaudible). This is really the issue of you have a grooming aid. You know probably some of it's going to get on the scalp, so now it's really a leave-on, and we've said that the safe concentration for a leave-on is 1 percent or below. So, I like not reopen as I said at the beginning, but how do we want to address this in the discussion to panelists as aware it's being used in hair grooming aids at 2 percent but we do not -- but we do not endorse anything over 1 percent, I guess, as a leave-on; something to that effect.

Ron? Tom? Does that sound good for a discussion?

DR. SLAGA: I think we have to.

DR. MARKS: Yes. And if we have data that suggests two percent and if industry has data then we can open it and make a safety assessment to increase the concentration.

Okay, do not reopen.

SPEAKER: Would this make it safe?

DR. BERGFELD: Excuse me, did you want to include in your discussion the guinea pig studies that we're doing at three percent that observed discreet patchy to moderate confluent erythema and
scaling at 24 and 48 hours? Thought to be non sensitizing.

DR. MARKS: Let me see if I have that on -- I remember that because it was done at three percent, that was above the safe limit of one percent, so I just -- that was part of the data which I presume went into -- was that a new study --

DR. BERGFELD: No.

DR. MARKS: -- since the report in the original report?

MR. BEST: The rinse off has also gone up one percent, right? The use -- because it was safe as used at five percent, now highest concentration at six percent.

DR. MARKS: Was there a concentration limit on the rinse offs? Did I miss that?

MR. BEST: I thought it was safe as used at the time, and the highest concentration back then was five percent. My guess, we're off.

DR. MARKS: Oh, I see what you're doing, you're going back and actually seeing the concentration of what was approved safe at that time.

MR. BEST: Right. So it's gone up one percent. I mean, you know.

MS. FIUME: Page 16.

DR. SHANK: Sixteen? Thank you.

DR. MARKS: And then I think it can be captured in the discussion as we note that both rinse off and leave-ons are higher than the one percent we actually mentioned in the conclusion and the other is in the use concentration back in the original report. Very good. Thank you.

MR. BEST: Thanks. And then some discussion of why you think it's okay. I mean is there a limit when it should stop? And this goes back to sort of the previous thing we talked about too where I just start getting some concern when we take off the caps and is there going to be this creep. So here we're seeing kind of the creep I was worried about before actually. So I mean you set a safe as used and it's exceeded the safe as used.

DR. MARKS: And that should be said in the discussion. Yes, I don't think we've taken the cap off as we say that safe as used at the time.
MR. BEST: Right. And so we're seeing growth though. They're going past safe as used, right, so I mean --

DR. MARKS: Right.

MR. BEST: -- are we seeing unsafe use? Is there a way to talk about that or do you say you still think it's safe or? Do we need some other kind of limit I guess is sort of my question as a consumer. I mean so generally it troubles me as sort of a consumer advocate when you guys are setting limits and then they're being exceeded. Because someone just said that -- and when it's an attorney that always makes you nervous, like you start seeing -- that's a slippery slope -- you start seeing people taking a little bit of liberty and you never know where the liberty stops.

DR. MARKS: My understanding is that then it comes under the purview of the FDA at that point. Linda, do you want to comment? If we aren't the enforcer, we're just making recommendations, and if it exceeds the recommendations then it would be up to the FDA to evaluate it and decide, just like the insufficient data. If an ingredient is being used and it's insufficient data -- now after two years is it -- that the ingredient is supposed to be removed?

MS. FIUME: The conclusion changes after two years.

DR. MARKS: So I don't know if I answered. I don't know if I answered your question. I think highlighting this discussion is what we do.

MR. BEST: What you all do. Yes.

DR. MARKS: And note that, not ignore that it is exceeding.

MR. BEST: Yes.

DR. MARKS: Yes.

DR. KATZ: And I was going to say from a regulatory standpoint that whatever advice is here is just advice.

DR. MARKS: Yes.

DR. KATZ: It's not regulatory binding.

DR. MARKS: Yes, that's -- thank you, Linda, for clarifying that.
DR. LANGE: Ultimately the company is responsible for ensuring the safety, so they would have to have data on file.

DR. MARKS: Right.

MR. BEST: Oh, no, no; and I understand that. I just mean from the way that we talk about it. I mean just that it's a slippery slope. So exactly what you said, drawing attention it is appropriate.

DR. GILL: But are we talking about changing the conclusion here? We said we weren't going to reopen.

DR. MARKS: Correct.

DR. EISENMANN: Wouldn't you really go to a -- if you changed the conclusion, say can formulate, be non irritating? I mean isn't the irritation the concern of sodium sulfate? I mean I think maybe part of the reason why there was a limit originally is because this was done during the period when you didn't have concentration of use surveys.

DR. BERGFELD: You couldn't have data.

DR. EISENMANN: Right. So you just did what the highest level that had been tested again. And I don't know if you noticed, when we were looking at the priority list calcium sulfate had 300 and some uses. There's calcium and potassium. You've already reviewed in separate reports magnesium and barium sulfates. Calcium and potassium have not been reviewed. Potassium doesn't have much use, but calcium does. So I don't know if you're trying to find words to make what the data -- our current use data and to build a conclusion. Maybe we should just reopen it and --

DR. HELDRETH: I strongly object to adding any other sulfates to this report. If you remember, two years ago Wilbur presented a report that was based on different sulfates and the discussion and consensus of the panel was that there is no read across or even inference between purely inorganic salts. And so therefore we should not group any other sulfates with this ingredient. Plus, on top of that, this is a re-review, so any additions to this report need to fit in the no brainer category, which means, at least in part, that the data already in the report needs to support the safety of any additions.

If there's no read across or inference, how would that be possible for calcium or
DR. MARKS: So on page 17 it says here, if you look under human, the next to the last sentence, in an experimental and sensitization using sodium sulfate effective concentration, 1 percent -- it's actually 1.01 from an aqueous bubble bath solution was tested via insult patches on 61 subjects and there was mild erythema in one subject with no reactions noted during the challenge. So to me that's a sensitization study and I wasn't part of the panel at that point. But I would assume the one percent limit is based on sensitization and not irritation. So to say formulate to be non irritating doesn't address the sensitization issue.

I still say don't reopen.

DR. SHANK: So do I.

DR. HILL: I agree with not reopening, but I do have a follow up question.

So if currently what he said, rinse off up to five percent -- so if somebody is marketing at six percent, at what point do we say, all right, if they've signed the Consumer Commitment Code and now they're breaching it -- potentially, unless they have data on file that shows everything is fine -- at what point might that two year clock start ticking if it's a report like this that isn't reopened? And similarly, that two percent, since the current conclusion is one percent and then they've gone over that, has the two year clock started ticking, will the two year -- or if the report is not opened there is no two year clock?

DR. HELDRETH: The two year clock has really nothing to do with this situation. That is for instances where the panel determines that something is insufficient data and we never get the response back.

In a case like this the panel already has a conclusion. If the panel reopened this and concluded it was insufficient, then a two year clock would begin. But in this case, you bring up the Consumer Commitment Code -- as Dr. Katz was mentioning, it's always the responsibility of the manufacturer to ensure the safety. This panel's recommendations can supplement that decision, but ultimately if they choose to go outside of the panel's recommendation they can do so as long as they're fulfilling FDA's requirement that they've assessed the safety themselves.
DR. HILL: Yes, I get that. I guess what I was asking is, is there -- when you say -- when the conclusions stands as it's safe up to one percent in a leave-on, for example, is there an implicit going over that is not necessarily safe?

In other words, let me restate that, is it implicitly saying the data are insufficient to support anything above that? Because I kind of think it is.

DR. GILL: Yes. And we don't have to (inaudible) to support safety above that.

MS. FIUME: Dr. Marks, would there be any desire -- because this conclusion came from a time when you didn't have concentration of use, that there is a (inaudible) -- would there be any desire to update the conclusion into our newer language of either safe and present practices in concentrations of use, or anything like that, based on the new data that were found, rather than just not reopen?

DR. MARKS: Where is the new data? You said page 17. Where was that? I saw the one percent.

MS. FIUME: There's a guinea pig maximization test on page 17.

DR. SHANK: Just above the human.

DR. BERGFELD: That the one I read before.

DR. MARKS: So what was the challenge dose? I'm looking at the top here. Not classified as sensitizer. This wasn't in the original --

MS. FIUME: Laura, this is new data, correct?

MS. SCOTT: This is --

DR. MARKS: Oh, okay.

MS. SCOTT: Desensitization test, the dermal sensitization test in your original report, it says there were no reactions observed at challenge. So one panelist had a reaction that was observed at induction. So I think that's why maybe the irritation was mentioned in the first report. I think that might be where the limit came from.

DR. MARKS: So in this guinea pig max test, I'm looking here, so intradermal induction (inaudible), in an epidermal inclusion challenge. So they were challenging with 50 percent?
MS. SCOTT: Mm-hmm.

DR. HILL: But what bugged me a little bit about this study is, is sodium sulfate even soluble in PEG 300? Because I doubt it.

As in are we somehow rigging the test by not by not doing an aqueous solution where it would be wonderfully and perfectly soluble.

DR. SHANK: It rolls off the skin.

MR. BEST: It's an occlusive patch.

DR. MARKS: Well, that would indicate -- thank you for point it out at least -- I mean that 50 percent would be safe.

DR. SHANK: And there's a 90 day dermal study. And in 90 days all they saw was mild dermatitis.

DR. MARKS: Mild. So then that would --

DR. SHANK: And that was 16 percent solution in water.

DR. MARKS: Reopen. Safe in present practice and use addressed is what you said.

DR. SHANK: Probably, yes.

DR. MARKS: Reopen.

SPEAKER: Am I missing something?

DR. MARKS: It was what I missed in terms of looking. I thought those were the old studies they based the original report on. So that's where I -- so I didn't look at them as closely. I was actually trying to justify the one percent safe. So the new conclusion would be safe in present practice and use. Okay.

DR. BERGFELD: And your discussion of that is going to include the addition of these two studies?

DR. MARKS: Absolutely. Yes, absolutely.

DR. BERGFELD: And the fact that there were -- are you going to say anything about the irritation?
DR. MARKS: Well, they're pretty high concentrations when you look at that. Let me
see, what page again was that?

DR. SHANK: Seventeen.

DR. MARKS: Seventeen?

SPEAKER: Seventeen.

DR. MARKS: The guinea pig max was at 50 percent in PEG 300, but I hear your
comments about this. And in the one that you were mentioning, Ron, is that on page 17 also?

DR. SHANK: Yes.

SPEAKER: Sixteen.

SPEAKER: Sixteen.

DR. SHANK: Sixteen.

DR. MARKS: Three month dermal, that's --

MS. SCOTT: It's under irritation and sensitization (inaudible).

DR. MARKS: And that was 16 percent? Since they aren't being used at those
concentrations I don't think we even have to mention irritation in the conclusion.

DR. BERGFELD: Would you mention that because they're not being used at high
concentrations, but rather in with X range, that irritations, sensitization would not be a problem or
something of that nature?

DR. MARKS: Yes, I think that's in the discussion. Yes.

DR. BERGFELD: Yes, okay. Good.

DR. MARKS: Okay. So tomorrow I'll change that. I assume I'm going to second a
motion to reopen with a conclusion safe, and the discussion now includes the two new studies we had since
the original report with validating safety as far as irritation and sensitization.

Okay. Anything more about this? Thank you so much for bringing that up and clarifying
it, Laura.

Okay. So second reopen safe, and the discussion includes the new irritation and
sensitization studies.

Any other comments?

MR. BEST: So ultimately it's very safe at very high concentrations it turns out?

DR. MARKS: Yes.

SPEAKER: Yes.

DR. MARKS: Exactly. You notice the -- it's amazing when you get the facts how things can change.

Okay.

DR. HILL: This is one of those I think popped up on the ingredient list (inaudible) let's not waste time on that, moving right along.

DR. MARKS: Next is Apple.

MINUTES FROM MARCH 2016 PANEL MEETING-SODIUM SULFATE-DAY2

DR. BERGFELD: We are moving on to the second one. The sodium sulfinate -- sulfate rather, Belsito, Dr. Belsito for reporting?

DR. BELSITO: So in 2000, when we reviewed the anhydrous and the decahydrate forms and concluded they were safe as used in rinse off formulations and safe use concentrations up to one percent in formulations. There was a time when we didn't have a concentration of use and would set the bars based upon the available data that we had. There has been a significant increase in frequency of use, 777 compared to 28 in 2000. Concentration and use has increased and in fact it has gone beyond above all leave ons that we had originally recommended so based upon all that, we felt we of course had to reopen the document to look at it.

We raised the question as to whether other sulfate salts could be added but felt that it was not appropriate to do that and just to continue with sodium sulfate and having made that decision, we decided to reopen and issue a tentative final as safe as used when formulated to be non-irritating.

DR. BERGFELD: Is there a second?

DR. MARKS: Second.

DR. BERGFELD: Is there any other discussion?
MS. SCOTT: I just want to mention one thing very quickly.

DR. BERGFELD: Go ahead.

MS. SCOTT: On page 17 of the PDF, there is an error in the guinea pigs cutaneously exposed to three percent sodium sulfate in PEG-300 during the maximization test so that three percent is actually the positive control substance and not the sodium sulfate.

DR. BELSITO: Yes.

MS. SCOTT: Okay, are there any other questions or discussion that I should mention?

DR. BERGFELD: Seeing none, I will call for the vote. All those to reopen the conclusion of safe? Thank you, unanimous.

(Motion Passed unanimously)

MINUTES FROM ORIGINAL REVIEW OF SODIUM SULFATE

June 1996
Drs. Belsito and Schroeter noted that there had been no response to the informal data request that was issued at the December 11-12, 1995 Panel meeting.

The Panel voted unanimously in favor of issuing an Insufficient Data Announcement on Sodium Sulfate with the following data requests:
(1) Human skin irritation study at concentration of use
(2) Concentrations of use

December 1996
Dr. Schroeter recalled that an Insufficient Data Announcement on Sodium Sulfate was issued at the June 3-4, 1996 Panel meeting, and that data addressing each request for information were received. The data requested were as follows: (1) Concentration of use and (2) Human dermal irritation at concentration of use. Dr. Schroeter also noted that his Team concluded that Sodium Sulfate is safe as used in cosmetics.

Dr. Belsito stated that his Team concluded that Sodium Sulfate is safe at concentrations up to 1.0% in leave-on products (based on negative results in the sensitization study included in the Draft Report) and safe as used in rinse-off products.

Dr. McEwen noted that, actually, a 1.25% aqueous solution of a bubble bath containing 80.8% Sodium Sulfate (effective concentration = 1.01%) was tested in the sensitization study. He recommended that the concentration limit for Sodium Sulfate in leave-on products should be stated accurately in the report conclusion based on this calculation.

Dr. McEwen confirmed with the Panel that the proposed concentration limit is based on negative results for skin irritation (Panel=s original concern) in the human repeated insult patch test.

The Panel unanimously concluded that Sodium Sulfate is safe at concentrations up to 1.0% in leave-on products and safe as used in rinse-off products, and voted in favor of issuing a Tentative Report with this conclusion.
Dr. Andersen noted that the derivation of the 1.0% concentration limit (actually 1.01% test concentration from sensitization study rounded off to nearest tenth) will be included in the report discussion.

**June 1997**

The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: Based on the available data, the CIR Expert Panel concludes Sodium Sulfate to be safe as used in rinse-off formulations, and safe up to 1% in leave-on formulations.
Amended Safety Assessment of Sodium Sulfate
as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: May 13, 2016
Panel Meeting Date: June 6-7, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst.

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*On the in-text Table references use “Ctrl + left click” in Word, or double (left) click in the PDF version, to link directly to the corresponding Table at the end of the document.
ABSTRACT
This is a safety assessment of Sodium Sulfate as used in cosmetics. Sodium Sulfate is reported to function in cosmetics as a viscosity increasing agent – aqueous. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the relevant new data for the ingredient. The Panel relied on relevant new data, including concentration of use, and considered data from the previous CIR report. The Panel concluded that Sodium Sulfate is safe in cosmetics in the present practices of use and concentrations described in this safety assessment when formulated to be non-irritating.

INTRODUCTION
In 2000, the Panel published a safety assessment of Sodium Sulfate, an ingredient that is reported in the International Cosmetic Ingredient Dictionary and Handbook to function as a viscosity increasing agent – aqueous in cosmetic formulations. In the original safety assessment, the Panel determined that Sodium Sulfate is safe as used in rinse-off formulations and safe for use up to concentrations of 1% in leave-on formulations, based on the data presented in the safety assessment and the standing that Sodium Sulfate is Generally Recognized as Safe (GRAS) when used as an indirect food additive (21CFR186.1797). The original safety assessment addressed both the anhydrous and decahydrate forms of Sodium Sulfate.

A search of published literature revealed one journal article with relevant information, which is summarized in this safety assessment (un-italicized text). For ease of comparison, italicized text throughout this report are data summarized from the original safety assessment. Additionally, updated frequency of use (2016) and updated concentration of use (2015-2016) data are reported here.

The original safety assessment is available at http://www.cir-safety.org/ingredients. Report summaries and unpublished data included in this safety assessment were found on the European Chemicals Agency (ECHA) website. The ECHA website provides summaries of information submitted by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY
Definition and Structure
Sodium Sulfate (CAS no. 7727-73-3 decahydrate; 7757-82-6 anhydrous) is the inorganic salt depicted in Figure 1.

![Figure 1. Sodium Sulfate](image)

Chemical and Physical Properties
Sodium Sulfate (anhydrous) is odorless and has the appearance of white crystals or powder. The decahydrate form is hydrated with 10 equivalents of water per sulfate ion. The formula weight of the anhydrous form is 142.04 Da and of the decahydrate form is 322.19 Da. Sodium Sulfate is soluble in water and glycerin and insoluble in alcohol.

Method of Manufacture
Neutralizing sulfuric acid with sodium hydroxide yields Sodium Sulfate.

Impurities
According to United States Pharmacopeia’s Food Chemical Codex, lead and selenium impurities are acceptable at not more than (NMT) 2 mg/kg (lead) and NMT 0.003% (selenium) in Sodium Sulfate used in food.

Natural Occurrence
In nature, Sodium Sulfate exists as the minerals thenardite and mirabilite.
USE

Cosmetic

The Panel evaluates the safety of the cosmetic ingredients included in this assessment based on the expected use of and potential exposure to the ingredients in cosmetics. The data received from the Food and Drug Administration (FDA) are collected from manufacturers through the FDA’s Voluntary Cosmetic Registration Program (VCRP), and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Personal Care Products Council (Council) in response to a survey of the maximum reported use concentrations by product category.

VCRP data obtained from the FDA in 2016 indicate that Sodium Sulfate is used in 777 cosmetic formulations\(^6\) compared to 28 uses reported originally\(^1\) (Table 1). Frequencies of use notably increased compared to originally reported values as follows (uses reported in 2016\(^6\) vs. originally reported uses\(^1\)): 86 vs. 13 leave-on; 661 vs. 3 rinse-off; 30 vs. 12 diluted for bath use; 35 vs. 7 incidental inhalation; 304 vs. 28 dermal contact; 215 vs. 15 mucous membrane. Uses not reported in the original assessment were reported in 2016\(^6\) as follows: 11 eye area uses; 1 incidental ingestion use; 2 deodorant uses; 127 hair non-coloring uses; 325 hair coloring uses; 11 nail uses; and 7 baby product uses.

The concentrations of use reported in the original safety assessment were not received from the FDA or the Council survey; they were reported from two separate submissions of unpublished data from industry.\(^1\) These data are considered to be a limited representation of concentrations in use at that time. The results of the concentration of use survey (Table 1) conducted by the Council in 2015-2016\(^7\) indicate that Sodium Sulfate is used at up to 96.4% (96.3% in original report\(^1\)) in diluted for-bath use formulations. In rinse-off formulations the highest maximum concentration of use for Sodium Sulfate based on the results of the 2015-2016 survey is 6%\(^7\) (5% reported originally\(^1\)). The highest maximum concentration of use reported for products resulting in leave-on dermal exposure is 2.0% in hair tonics and other hair grooming aids\(^7\) (0.5% in facial lotion and facial toner reported originally\(^1\)). In the product category, hair non-coloring, the highest maximum concentration of use reported increased from 1%\(^1\) (original report) to 2.5% in 2015-2016.\(^7\) There was no substantial increase in concentration of use from the original report compared to 2015-2016 reported use for the product categories associated with dermal contact and mucous membrane exposure. Highest maximum use concentrations not reported in the original assessment have been reported in 2015-2016 as follows: eye area (in eye make-up remover up to 0.0064%), incidental ingestion (in dentifrices up to 0.83%), deodorant (up to 0.3%), hair coloring (up to 3.8%), nail (up to 0.5%), and baby products (in baby shampoos up to 0.29%).

In some cases, reports of uses were received in the VCRP, but concentrations of use data were not provided. For example, Sodium Sulfate is reported to be used in 4 “other hair preparation” formulations (no further details provided)\(^6\), but no use concentration data were reported. In other cases, no uses were reported in the VCRP, but concentration of use data were received from industry; Sodium Sulfate had no reported uses in the VCRP, but a use concentration in hair bleach at up to 3.8% was provided in the industry survey\(^7\). Therefore, it should be presumed that there is at least one use in every category for which a concentration or a frequency of use is reported.

Sodium Sulfate was reported to be used in cosmetic sprays and powders including, face powders (up to 0.5%), fragrance preparations (up to 0.03%), and hair tonics (up to 2.0%) and could possibly be inhaled.\(^7\) 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 sprays.\(^k\)\(^11\). 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.\(^8\)\(^9\) Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.\(^12\)\(^14\)

Sodium Sulfate anhydrous (7757-82-6) is not restricted from use in any way under the rules governing cosmetic products in the European Union.\(^15\)

Non-Cosmetic

The Code of Federal Regulations section on indirect food additives that are GRAS indicates that Sodium Sulfate is used in components of paper and paperboard used in food packaging, as well as in the cotton and cotton fabric in dry food wrapping (21CFR186.1797). Sodium Sulfate is listed as an indirect food additive with no limitations in substances used as “basic components in single and repeated use food contact surfaces” in the section referring to
cellophane (21CFR177.1200). It is a direct food additive that appears under “Miscellaneous” in the section referring to chewing gum base substances (21CFR172.615); it is recorded as a secondary direct food additive with no limitations for use in boiler water additives used to prepare steam that comes into contact with food (21CFR173.310). Mentioned as a color additive that is exempt from certification, Sodium Sulfate can be utilized as a food-grade salt, in accordance with good manufacturing practice, to assist in caramelization (21CFR73.85).

The *Food Chemicals Codex* lists Sodium Sulfate as an agent used in caramel production.\(^5\)

Sodium Sulfate is listed as an ingredient on drug labels for colonic preparations because of its laxative effect.\(^16\) Sodium Sulfate is included as an inactive ingredient in FDA approved drug products at the following concentrations (exposure routes noted in parenthesis): up to 1.2% (ophthalmic), up to 0.03% (inhalation), up to 182 mg (oral), and up to 1.14% (intravenous).\(^17\)

**TOXICOKINETIC STUDIES**  
**Absorption, Distribution, Metabolism, and Excretion (ADME)**

**Animal**

**Oral**

*Oral studies conducted in rats showed that Sodium Sulfate was absorbed by the gut. One experiment noted 57-74% of radioactive Sodium Sulfate (Na\(^2\)\(^{35}\)SO\(_4\)) was excreted in the urine within 24 hours post-administration.\(^1\) In another study 90% of the dose of Sodium Sulfate (Na\(^2\)\(^{35}\)SO\(_4\)) was recovered in the urine within 24 hours of oral administration.*

**Intraperitoneally**

*A test in which radioactive Sodium Sulfate (Na\(^2\)\(^{35}\)SO\(_4\)) was intraperitoneally administered (180-330 g) to rats, 85% of the dose was detected in urine and, with the inclusion of fecal excretion, 95% of the dose was recovered in 120 hours.\(^1\) Nearly complete elimination of the dose was observed by 48 hours in blood, liver, and brain. In bone and bone marrow tissue samples substantial concentrations were still present up to 120 hours after administration.*

**Human**

**Oral**

*In human subjects, experiments have been conducted to measure the recovery of free sulfate in the urine after oral administration of Sodium Sulfate.\(^1\) The sulfate detected in urine 24 and 72 hours after dosing (18.1 g of decahydrate Sodium Sulfate administered in a single dose or 4 equally divided doses) was 36.4% and 53.4% (single dose) and 43.5% and 61.8% (divided dose), respectively. Subjects who were administered a single dose of 18.1 g Sodium Sulfate reported severe diarrhea between 2-24 hours following dosing.*

**Sulfate-Mediated Drug Metabolism**

Sodium Sulfate can increase the elimination rate of high doses of acetaminophen by providing inorganic sulfate to reduce acetaminophen toxicity, as shown in some animal studies.\(^1\) In humans, the liver, primarily, and the kidneys and intestines, secondarily, metabolize acetaminophen.\(^18\) In the body, acetaminophen is mostly converted to metabolites, which are excreted in the urine as: inactive acetaminophen glucuronide (52-57% of dose), inactive acetaminophen sulfate conjugates (30-44% of dose), and very reactive N-acetyl-p-benzoquinone imine (NAPQI, 5-10% of dose). NAPQI is the main metabolite that causes acetaminophen-induced hepatotoxicity. NAPQI binds to glutathione and is excreted in the urine as cysteine and mercapturic acid conjugates. At extremely high doses of acetaminophen (> 4 g/day in humans) the sulfation pathway, and eventually the glucuronidation pathway, become saturated, leading to the depletion of glutathione and the accumulation of NAPQI. The excess unconjugated NAPQI interacts with critical proteins to cause ion-channel imbalances, loss of cellular energy production and, ultimately, cell death. The antidote for acetaminophen poisoning is N-acetylcysteine (NAC) administered orally or intravenously, because it delivers glutathione and facilitates the sulfation pathway to elevate the elimination rate of NAPQI from the body.
**TOXICOLOGICAL STUDIES**

**Acute Toxicity Studies**

**Animal**

**Oral**

A study following Organization for Economic Co-operation and Development (OECD) Guideline 423-Acute Oral Toxicity-Acute Toxic Class Method, using Good Laboratory Practice (GLP), was conducted to evaluate the acute oral toxicity of Sodium Sulfate in Wistar rats. After fasting (17-20 hours), 1 group of 3 female rats (no controls) was administered one dose of 2000 mg/kg Sodium Sulfate in polyethylene glycol (PEG 300) by gavage. No pertinent clinical signs or Sodium Sulfate associated deaths were noted 48 hours following administration, therefore another group of 3 female rats (no controls) were dosed the same as the first group. All 6 rats were observed for 15 days. No effects on body weight or gross pathology were observed. One rat died as a result of the gavage procedure immediately after dosing; this was not Sodium Sulfate treatment related. An LD$_{50}$ > 2000 mg/kg Sodium Sulfate for female rats was reported.

**Inhalation**

Research on intubated anesthetized dogs breathing aerosol generated from a 0.1% Sodium Sulfate solution (particles size 0.1-0.2 µm) for 7.5 minutes in one study, and 0.5% Sodium Sulfate solution for 4 hours in another experiment, resulted in no significant change in respiratory functions. In sheep exposed to 0.1% Sodium Sulfate solution for 20 minutes or those exposed to a 0.3% Sodium Sulfate solution for 4 hours, no significant changes were observed. Studies were also conducted on guinea pigs (1 hour exposure to 0.90 mg/m³ Sodium Sulfate, 0.1 µm particle size) and rabbits (1 hour exposure to 2000 µg/m³ Sodium Sulfate) without notable adverse effects.

**Human**

**Inhalation**

Human subjects (n=5 healthy, n=5 asthmatic) were exposed to Sodium Sulfate aerosol (mass median aerodynamic diameter of 0.5 µm) up to 3 mg/m³ for 10 minutes. Results indicated no difference in pulmonary function up to 1 hour after exposure to Sodium Sulfate compared to sodium chloride (control) except in 2 asthmatics showing a 15-20% reduction in forced exhalation volume (FEV$_1$). In a subsequent test in human subjects (n=6 healthy, n=6 asthmatic) exposed to Sodium Sulfate aerosol (3 mg/m³ for 10 minutes; lung function measurements recorded for 3 hours post-exposure) there were no adverse effects on pulmonary function compared to sodium chloride (control). Two asthmatics exhibited a 15-20% drop in FEV$_1$ following exposure to Sodium Sulfate or sodium chloride.

**Short-Term Toxicity Studies**

**Animal**

**Oral**

An experiment, lasting 4 weeks, in weanling rats fed up to 138 mmol Sodium Sulfate/kg basal diet showed no significant differences between the control group with regards to: weight gain, feed in-take, feed-gain ratio, water intake, hemoglobin levels, red blood cell count, white blood cell count, serum protein, alkaline phosphatase, and inorganic phosphatase concentrations. Small intestine length and color and gastrointestinal organ weights were also unaffected.

A study was conducted in 28-day old weaned crossbred pigs (Landrace or Yorkshire cross, n = 415 tested in study including controls) for 4 weeks to evaluate the effects of Sodium Sulfate and Magnesium Sulfate. Sodium Sulfate or Magnesium Sulfate or both were administered orally in drinking water at 600, 1200, or 1800 mg/L ad libitum. In the fourth week of exposure, there was a statistically significant body weight gain increase with increasing sulfate concentrations to pigs administered either 600 mg/L or 1800 mg/mL Sodium Sulfate or 600 mg/L or 1800 mg/L Magnesium Sulfate (results for 1200 mg/L Sodium Sulfate or 1200 mg/L Magnesium Sulfate are not reported during the fourth week) compared to the control group. When Sodium Sulfate and Magnesium Sulfate were administered in the same test group this trend was not observed at any of the concentrations tested (e.g. combined Sodium Sulfate and Magnesium Sulfate at 600 mg/L in one test group; combined Sodium Sulfate and Magnesium Sulfate at 1200 mg/L in another test group, etc.). There were no differences in feed-to-body-weight gain ratios in treated groups compared to the control group. At 1800 mg/L total sulfate concentration (combined Sodium Sulfate and Magnesium Sulfate; distribution not specified) a statistically significant increase in water consumption was observed. A statistically significant increase in incidence of diarrhea was correlated with total sulfate concentrations (combined...
Sodium Sulfate and Magnesium Sulfate; distribution not specified) of 600, 1200, and 1800 mg/L and determined not to be attributed to high concentrations of common post-weaning pathogens. This high-sulfate-content water consumption, resulting in increased incidence of diarrhea, did not negatively impact growth rate, increase mortality, or increase post-weaning pathogens. The deaths of 4 pigs (mortality rate 0.96%) during the study were not attributed to sulfate treatment; 3 died of enterotoxigenic *Escherichia coli* and 1 was euthanatized because of weight loss and lack of response to therapeutic interventions.

**Human**

*Oral*

There was a 14 day study in subjects (with a history of colonic polyps) that were orally administered 4-6 g/day of Sodium Sulfate. Results yielded no adverse effects.²

**Subchronic Toxicity**

**Animal**

*Dermal*

A 90-day dermal toxicity study was conducted using methods similar to OECD Guideline 411-Subchronic Dermal Toxicity to determine the effects of Sodium Sulfate on New Zealand White rabbits (n=5 males/5 females per test group).³ During the study Sodium Sulfate was administered percutaneously as a positive control in 65 treatments (no further details on dermal-exposure method were provided) at 2 mL/kg/day (16% w/w Sodium Sulfate solution). The control (water) was administered percutaneously at 2 mL/kg/day. Results indicated that clinical signs and mortality, body weight and weight gain (animals were reported to gain weight in this study), organ weights, and gross pathology were unaffected by treatment. Hematology tests revealed no statistically significant differences in results between control and test groups, except for a statistically significant increase in MCV (mean corpuscular volume) and MCH (mean corpuscular hemoglobin) measurements for test group females compared to control females. However, the researchers concluded this was not “biologically significant” because the rabbits’ individual values were within normal ranges. Histopathology results were non-neoplastic with the only test-related lesion noted to be subacute dermatitis (see Irritation and Sensitization section for further details). Observations were normal, related to spontaneous disease, or incidental lesions.

**DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES**

*Oral*

Experiments conducted in pregnant ICR/SIM mice orally administered (via intubation) 2800 mg/kg/day Sodium Sulfate on days 8 through 12 of gestation showed no maternal toxicity.¹ No resorptions were observed in treated or control groups; all neonates in the treated group survived from days 1-3. Average birthweight of treated neonates was statistically significantly greater than controls. The researchers considered this to be a positive result for Sodium Sulfate, despite the lack of maternal toxicity in the treated group. However, the researchers acknowledged that, with the absence of published teratogenic data for orally administered Sodium Sulfate, they could not confirm the validity of the positive results.

Studies were conducted in Wistar rats to evaluate the effect of Sodium Sulfate on reproduction.⁴ The first study (non-GLP) was used to determine the exposure concentrations for the second (OECD Guideline 421-Reproduction/Developmental Toxicity Screening Test, GLP), more comprehensive experiment. Groups of 3 male and 3 female rats were dosed with 0, 100, 300, and 1000 mg/kg/day Sodium Sulfate. Both sexes were dosed by gavage for 14 days pre-pairing, during pairing (14-day max), and up to 1 day before necropsy for males and up to day 13 of gestation for females. Males were killed after at least 28 days of dosing and females were killed on day 14 of gestation. No rats died prior to necropsy. Endpoints including food consumption, body weights, reproductive performance, and gross pathology were unaffected by Sodium Sulfate in either sex during the duration of study. For females, endpoints including number of corpora lutea, pre- and post-implantation loss, and number of live embryos were also unaffected by treatment with Sodium Sulfate. The only clinical observation to note, at 1000 mg/kg/day Sodium Sulfate, was soft feces in both sexes on day 11 of the pre-pairing period through day 3 after pairing (males) and days 2 or 3 of gestation (females). Gross examination yielded no abnormal findings.

Another experiment was conducted to determine the effects of Sodium Sulfate on reproductive performance of Wistar rats.⁵ Similar parameters were monitored as in the first experiment summarized above (same dose rates, i.e., 0, 100, 300, 1000 mg/kg/day Sodium Sulfate) with the following exceptions: each group contained 10 males and 10 females; males were killed after at least 28 days of treatment, females were allowed to give birth and rear their litters
for 4 days post-partum, and females and pups were killed on day 4 post-partum. If the females did not give birth when expected (day 21 of gestation) they were killed by day 25 of gestation. Parental endpoints of clinical signs, body weight, food consumption, reproductive function (sperm measures), reproductive performance, fertility index, conception rate, organ weights, gross pathology, and histopathology were unaffected by Sodium Sulfate. No parental deaths were reported prior to scheduled necropsies. The duration of gestation, corpora lutea count, implantation rate, post-implantation loss, duration of gestation, and litter size at first litter check were unaffected by Sodium Sulfate. One pup from the control group died on day 3. Offspring endpoints of viability, clinical signs, body weight, and gross pathology were unaffected by Sodium Sulfate. Upon gross examination of the pups no abnormal findings were reported. A general no observed effect level (NOEL), as well as reproduction/developmental toxicity NOEL, was reported to be 1000 mg/kg/day.

**GENOTOXICITY STUDIES**

*In Vitro*

An experiment examining Sodium Sulfate for genotoxicity was negative in a microscreen assay (275 µg/well Sodium Sulfate) evaluating bacterial DNA damage by measuring prophage induction into Escherichia coli.1 Another test evaluating Sodium Sulfate on Syrian hamster embryo cells was determined to be negative for enhanced transformation of the cells by a simian adenovirus (SA7). An Ames test was conducted to evaluate the effect of Sodium Sulfate (312.5 to 5000 µg per plate with 4 dilutions) on *Salmonella typhimurium* TA1535, TA1537, TA100, and TA98, both with and without metabolic activation.4 The results were negative for genotoxicity. No cytotoxicity was observed at the concentrations tested.

An *in vitro* mammalian chromosome aberration test (GLP compliant) was performed in Chinese hamster lung fibroblasts (V79) in accordance with OECD Guideline 473 – *in vitro* Mammalian Chromosome Aberration Test.4 The test was performed with and without metabolic activation. The exposure duration of experiment 1 was 4 hours with and without metabolic activation. The exposure durations of experiment 2 were 4 hours with metabolic activation and 18 hours without metabolic activation. Both experiments used deionized water as the vehicle. Test concentrations with and without metabolic activation in experiment 1 were 11.1, 22.2, 44.4, 88.8, 177.5, 355.0, 710.0, and 1420.0 µg/mL Sodium Sulfate. In experiment 2 with activation, concentrations tested were 177.5, 355.0, 710.0, and 1420.0 µg/mL Sodium Sulfate. Test concentrations without metabolic activation in experiment 2 were 22.2, 44.4, 88.8, 177.5, 355.0, 710.0, and 1420.0 µg/mL Sodium Sulfate. Negative solvent/vehicle controls and positive controls were used.

Outcomes revealed that Sodium Sulfate did not induce structural chromosome aberrations in V79 cells of the Chinese hamster *in vitro* (non-clastogenic) up to 1420.0 µg/mL.4 No cytotoxic effects or biologically relevant increase in the number of cells containing structural chromosome aberrations were noted (with or without metabolic activation). No biologically relevant increase in the rate of polyploid cells was found. Appropriate vehicle and positive controls yielded expected results.

An *in vitro* mammalian cell gene mutation assay test (GLP compliant) was conducted in mouse lymphoma L5178Y cells in accordance with OECD Guideline 476 – *in vitro* Mammalian Cell Gene Mutation Test.4 The test was performed with and without metabolic activation. The exposure duration of experiment 1 was 4 hours with and without metabolic activation. Experiment 2 exposure durations were 24 hours without metabolic activation and 4 hours with metabolic activation. The concentrations tested in experiments 1 and 2, both with and without metabolic activation, were 88.8, 177.5, 355, 710, and 1420 µg/mL Sodium Sulfate (deionized water was vehicle/solvent used). Negative solvent/vehicle controls and appropriate positive controls were used. Results were negative for genotoxicity and negative for cytotoxicity, whether in the absence or the presence of metabolic activation. Therefore, Sodium Sulfate was not found to induce mutations in the mouse lymphoma thymidine kinase locus assay (cell line L5178Y).

**CARCINOGENICITY STUDIES**

*Co-Carcinogenicity*

In one study Sodium Sulfate was shown to inhibit the carcinogenicity of N-hydroxy-N-2-fluorenylacetamide (N-OH-FAA) or increase the inhibitory effect of p-hydroxyacetanilide in rats fed 0.89 mmole/kg N-OH-FAA concurrently with 3 equivalents of Sodium Sulfate.1 However, another experiment in which rats were fed 1.34 mmole/kg N-OH-FAA and 3 equivalents of Sodium Sulfate showed no additional effect on the inhibitory actions of p-
hydroxyacetanilide. A test in rats that were fed a carcinogen (0.06% 3'-methyl-4-dimethylaminoazobenzine) and Sodium Sulfate (0.84%) resulted in increased risks of developing multiple neoplasms and metastatic neoplasms. A study in mice that were co-administered Sodium Sulfate and an inhibitor in their diet in equimolar ratios resulted in partially restoring leukemogenicity of N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide (NFTA). A test in which rats were fed Sodium Sulfate and then were injected with dimethylhydrazine (DMH) resulted in fewer colon tumors in rats treated with Sodium Sulfate plus DMH compared to those treated with only DMH.

**DERMAL IRRITATION AND SENSITIZATION STUDIES**

**Irritation**

**Animal**

A 90-day dermal toxicity study was conducted using methods similar to OECD Guideline 411-Subchronic Dermal Toxicity to determine the effects of Sodium Sulfate on New Zealand White rabbits (n=5 males/5 females per test group). Sodium Sulfate was percutaneously administered as a positive control in 65 treatments spanning 91 days (no further details on dermal-exposure method were provided) at 2 mL/kg/day (16% w/w Sodium Sulfate solution). Water was administered percutaneously as the control at 2 mL/kg/day. An effect occurred in 3 control-group rabbits showing mild subacute dermatitis and in the 16% Sodium Sulfate-group in 8 rabbits showing mild to moderate subacute dermatitis. The lowest observed adverse effect level (LOAEL) for Sodium Sulfate in this study was 2 mL/kg/day of a 16% (w/w) aqueous Sodium Sulfate solution.

An in vivo (GLP) study was conducted in accordance with OECD Guideline 404 – Acute Dermal Irritation/Corrosion, to evaluate the effect of Sodium Sulfate on rabbits (n=3). Occlusive patches containing 500 mg Sodium Sulfate in polyethylene glycol (PEG) 400 were applied for 4 hours. Dermal application sites were examined for up to 14 days post-exposure (no further details provided). Results showed that Sodium Sulfate was non-irritating.

**Human**

Several occlusive patch tests containing Sodium Sulfate were conducted in human subjects. One patch test using the equivalent of 9.7% Sodium Sulfate in a bath bead formulation yielded results with only 1 of 19 subjects reacting with ± (first non-zero grade on a 0 to 4± scale) Three 24-hour patches of a bar soap flake formulation containing 5.84% Sodium Sulfate (effective concentration of 0.1168%) resulted in mild irritation in 11 out of 13 subjects. An experiment containing an effective Sodium Sulfate concentration of 1.8% in a patch, comparable to 200 times the expected use of a children’s powdered bubble bath preparation, showed 7 subjects had mild erythema and 8 had dryness (±) out of 20 subjects tested. A test with a Sodium Sulfate patch concentration corresponding to 0.004% in an aqueous solution cleansing bar resulted in various exposures to all 35 subjects in a 21 day study. Overall the formulation was deemed to be mildly irritating.

**Sensitization**

**Animal**

A Guinea Pig Maximization Test (GLP) in male albino Dunkin-Hartley guinea pigs was conducted to determine the allergenic potential of dermal exposure to Sodium Sulfate. The OECD Guideline 406 – Skin Sensitization was followed. Appropriate negative and positive controls were used yielding expected results. Three phases of the experiment included: intradermal induction (25% Sodium Sulfate in PEG 300), epidermal induction (75% Sodium Sulfate in PEG 300), and epidermal occlusive challenge (50% Sodium Sulfate in PEG 300). There were 5 control animals, 10 test animals, 1 animal used for the intradermal pretest, and 2 animals used for the epidermal pretest. On Test Day 1 there were 3 pairs of intradermal injections (0.1 mL/site) given within the 4 x 6 cm clipped, hair-free zone of scapular region dorsal skin. Test groups received 1:1 (v/v) Freund’s Complete Adjuvant and physiological saline mixture, 25% Sodium Sulfate in PEG 300, or 25% Sodium Sulfate in a 1:1 (v/v) mix of Freund’s Complete Adjuvant and physiological saline. Control groups received 1:1 (v/v) mix of Freund’s Complete Adjuvant and physiological saline, PEG 300, or 1:1 (w/w) mix of PEG 300 in a 1:1 (v/v) mix of Freund’s Complete Adjuvant and physiological saline.

The epidermal induction was conducted on Test Day 8. A week following intradermal injections, a 2 x 4 cm occlusive 48-hour patch with 75% Sodium Sulfate in PEG 300 (~0.3 g Sodium Sulfate) was placed on each injection site. The control group guinea pigs were treated similarly except no Sodium Sulfate was present in the PEG 300 (~0.3 mL) solution. The injection sites were examined for erythema and edema 24 and 48 hours after injection.
The challenge was performed on test and control group guinea pigs on test day 22, following a 2 week non-treatment period after the completion of the induction phase. Two 24-hour occlusive patches (3 x 3 cm) with 0.2 mL of 50% Sodium Sulfate in PEG 300 were placed on the left flank and PEG 300 only (~0.2 mL) placed on the right flank. Results indicated no toxic signs or local skin effects in the surviving guinea pigs of the control or test group. During this study there were no deaths attributable to Sodium Sulfate exposure and no control or test group animals showed toxic signs; animals were not necropsied. One animal was euthanized because of a prolapsed anus and blood loss, which were not treatment related. Body weight and clinical signs were unaffected by Sodium Sulfate. Concluding remarks were that Sodium Sulfate was not classified as a skin sensitizer (in accordance with Regulation EC No. 1272/2008).

**Human**

In an experiment on sensitization using a Sodium Sulfate effective concentration of 1.01% (100 times greater than normal use levels) from an aqueous bubble bath solution was tested via insult patches on 61 subjects. The only notable result was a mild erythema reaction in one subject during induction with no reactions noted during challenge.

**OCULAR IRRITATION STUDIES**

**Animal**

Direct application of up to 0.1 mL sodium carbonate-Sodium Sulfate granular mixture (1:1, w/w) to the corneas of 3 rabbits resulted in moderate ocular irritation.

**CLINICAL STUDIES**

**Occupational Exposure**

Inhalation

For workers with occupational exposure to Sodium Sulfate dust at concentrations up to 150 mg/m³ no abnormalities associated with long-term exposure (between 2 months and 31 years) were found when cardiorespiratory, gastrointestinal, or hepatorenal parameters were measured compared to the general population. Additionally, lung function, serum sulfate, calcium and electrolytes were normal.

**SUMMARY**

The CIR Expert Panel originally concluded that Sodium Sulfate was safe as used in cosmetic rinse-off formulations and safe up to 1% in leave-on formulations. This conclusion was based on several factors, including the GRAS status of Sodium Sulfate used as an indirect food additive, data submitted by the cosmetics industry addressing dermal irritation and sensitization, and results from a clinical sensitization study evaluating repeated, prolonged exposure in which 1 in 61 subjects exhibited mild erythema in response to a 1.01% sodium-sulfate-containing patch applied for 24 hours.

Sodium Sulfate is listed as an ingredient on drug labels for colonic preparations. It is included as an inactive ingredient in FDA approved drug products in ophthalmic, inhalation, oral, and intravenous preparations.

The current frequency of use of Sodium Sulfate reported in cosmetic formulations (777 uses) is a considerable increase from the 28 uses reported originally. The highest reported frequencies of use are in hair dyes and colors (320 uses) in the current VCRP data and were in bubble baths (11 uses) in the original report. The frequencies of use in cosmetic formulations reported for the following categories are (uses reported in 2016 vs. uses reported in originally): 86 vs. 13 leave-on; 661 vs. 3 rinse-off; 30 vs. 12 diluted for bath use. The product categories for which no uses were reported in the original assessment have reported uses in the 2016 survey for: eye area, incidental ingestion, deodorant, hair non-coloring, hair coloring, nail, and baby products.

The concentrations of use reported in the original safety assessment are a limited representation of concentrations in use at that time; the concentrations originally reported were from two separate submissions of unpublished data from industry and not from the FDA VCRP or the Council industry survey. There is no substantial change from the original report, specifying concentrations of use up to 5% in rinse-off formulations and up to 96.3% in cosmetic formulations diluted for bath use, compared to current uses. The original safety assessment reported a concentration of use in leave-on dermal exposure cosmetic products to be 0.5%, as compared to the currently reported highest maximum use concentration of 2%. The product categories for which no concentrations were reported in the
original assessment, but have concentrations reported in the 2015-2016 survey for: eye area, incidental ingestion, incidental inhalation, deodorant, hair coloring, nail, and baby products.

In an acute oral toxicological study conducted in rats, no significant effects from Sodium Sulfate were noted in test animals administered Sodium Sulfate at 2000 mg/kg; this study reported an LD₅₀ > 2000 mg/kg/ in female rats.

During a 3-month repeated-dose dermal toxicity study in rabbits, clinical signs and mortality, body weight and weight gain, organ weights, and gross pathology were unaffected by percutaneously administered Sodium Sulfate (2 ml/kg/day; 16% w,w). Hematology results were not biologically significant; histopathology results showed the only treatment-related skin lesions were subacute dermatitis. In a 4-week repeated-dose study in nursery pigs orally administered Sodium Sulfate in their water ad libitum the observations noted were: increased water intake at 1800 mg/L Sodium Sulfate, increased incidence of diarrhea at 600, 1200, and 1800 mg/L Sodium Sulfate, but no negative effect on growth rate nor increased mortality at any of these concentrations.

Reproductive and developmental toxicity experiments in rats (administration by gavage) reported no abnormal results other than soft feces in both male and female rats administered Sodium Sulfate by gavage at dose rates up to 1000 mg/kg/day. Another study in rats dosed with Sodium Sulfate up to 1000 mg/kg/day by gavage concluded no abnormal findings, and reported a 1000 mg/kg/day NOEL for both general and reproductive/developmental toxicity endpoints.

Genotoxicity studies conducted on S. typhimurium, Chinese hamster lung fibroblasts (V79), and mouse lymphoma L5178Y cells testing Sodium Sulfate up to 5000 µg per plate (with 4 dilutions), 1420.0 µg/mL, and 1420 µg/mL, respectively, were negative for genotoxicity and cytotoxicity. The test on Chinese hamster lung fibroblast cells was also negative for polyploid cells.

In dermal irritation and sensitization experiments, 8 rabbits exhibited mild to moderate subacute dermatitis when percutaneously exposed to 16% (w/w) Sodium Sulfate at 2 mL/kg/day, which was the reported LOAEL. Three control rabbits exhibited mild subacute dermatitis in this study. In an occlusive coverage test, 4 hour duration, 500 mg Sodium Sulfate was determined to be non-irritating to rabbits. Sodium Sulfate was deemed to be non-sensitizing to guinea pig skin in a Guinea Pig Maximization test using a challenge dose of 50% Sodium Sulfate (in PEG 300).

**DISCUSSION**

The Panel decided to reopen the Final Report on the Safety Assessment of Sodium Sulfate based on the significant increase in reported frequency of use (777 uses reported in 2016 compared to 28 uses originally) and the increase in highest maximum use concentration reported for leave-on products (to up to 2% in hair tonics and other hair grooming aids), which exceeds the leave-on use concentration noted in the original conclusion (safe up to 1% in leave-on formulations).

The dermal irritation data presented in this safety assessment, including data summarized from the original report, show mixed results. Test results in animals and humans, at various doses evaluated, showed no to moderate irritation. Sensitization study results showed that Sodium Sulfate was non-sensitizing in both animals (challenge dose of 50% Sodium Sulfate) and humans (1% Sodium Sulfate tested). Given these results, the Panel specified that cosmetics that contain this ingredient should be formulated to be non-irritating.

Moderate ocular irritation was observed in an experiment, reported in the original assessment, in which Sodium Sulfate (1:1, w/w, granular mixture of Sodium Sulfate: sodium carbonate) was instilled into the corneas of rabbits. The highest reported maximum use concentration of Sodium Sulfate in cosmetic products used in the eye area (up to 0.0064% in eye make-up removers) is orders of magnitude less than the Sodium Sulfate concentration reported to be used as an inactive ingredient in FDA-approved ophthalmic drug products (up to 1.2%) and the concentration that produced moderate eye irritation in the rabbits tested. Thus, the potential for ocular irritation from exposure to Sodium Sulfate in cosmetic products is very low.

The Panel discussed the issue of incidental inhalation exposure from fragrance sprays, hair tonics, and face powders. The Panel considered pertinent data from the original report, for test animals and human subjects, indicating that incidental inhalation exposures to Sodium Sulfate in such cosmetic products would not cause adverse health effects. From the original assessment, several acute inhalation toxicity studies evaluating the effects of Sodium Sulfate (up to 0.5% or up to 2000 µg/m³; particle sizes 0.1-0.2 µm, when specified) in animals reported no significant changes in respiratory functions. For workers with occupational exposure (2 months to 31 years) to Sodium Sulfate dust (up to 150 mg/m³) no abnormalities (cardiorespiratory, gastrointestinal, hepatorenal, pulmonary) were associated with long-term exposure as reported in the original assessment. Although particles appear to have reached the lungs in
these studies, the sizes of the particles used were either clearly within the respirable range (i.e., \( \leq 10 \, \mu m \)) or were not reported. Sodium Sulfate is reportedly used at concentrations up to 2% in cosmetic products that may be aerosolized and up to 0.5% in face powder that may become airborne. The Panel noted that droplets/particles produced in cosmetic aerosols and loose-powder cosmetic products would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, 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.

Data presented in this safety assessment show an absence of substantial systemic toxicity for Sodium Sulfate administered at high doses in acute oral and repeated-dose dermal and oral exposure studies. Sodium Sulfate was non-toxic in development and reproductive tests. Genotoxicity was negative in an Ames test and in experiments evaluating chromosome aberrations and gene mutations. Sodium Sulfate was found to be non-sensitizing in a Guinea Pig Maximization Test. These results are in agreement with toxicity data reported in the original safety assessment and affirm the lack of toxicity of Sodium Sulfate for use in cosmetics.

**CONCLUSION**

The CIR Expert Panel concluded that Sodium Sulfate is safe in cosmetics in the present practices of use and concentrations described in this safety assessment when formulated to be non-irritating.
Table 1. Current and historical frequency and concentration of use of Sodium Sulfate according to duration and exposure

<table>
<thead>
<tr>
<th>Duration of Use</th>
<th># of Uses</th>
<th>Max Conc of Use (%)</th>
<th>2016(^a)</th>
<th>2000(^b)</th>
<th>2015-2016</th>
<th>2000(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals(^*)</td>
<td>777</td>
<td>28</td>
<td>0.0000002-96.4</td>
<td>0.1-96.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leave-On</td>
<td>86</td>
<td>13</td>
<td>0.000002-2.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rinse-Off</td>
<td>661</td>
<td>3</td>
<td>0.0000002-6.0</td>
<td>0.1-5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diluted for (Bath) Use</td>
<td>30</td>
<td>12</td>
<td>0.00053-96.4</td>
<td>3.5-96.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exposure Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Area</td>
<td>11</td>
<td>NR</td>
<td>0.000046-0.0064</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental Ingestion</td>
<td>1</td>
<td>NR</td>
<td>0.00015-0.83</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental Inhalation-Spray</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>possible: 35(^a); 13(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>possible: 7(^b); 3(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>spray: 0.0088-0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>possible: 0.00015-2.0(^a); 0.006(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental Inhalation-Powder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>possible: 13(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>possible: 3(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>powder: 0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>possible: 0.006(^b); 0.00023-0.54(^c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal Contact</td>
<td>304</td>
<td>28</td>
<td>0.0000002-96.4</td>
<td>0.5-96.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deodorant (underarm)</td>
<td>2(^a)</td>
<td>NR</td>
<td>0.000014-0.3 (not spray)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair - Non-Coloring</td>
<td>127</td>
<td>NR</td>
<td>0.0000002-2.5</td>
<td>0.1-1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair-Coloring</td>
<td>325</td>
<td>NR</td>
<td>0.000051-3.8</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail</td>
<td>11</td>
<td>NR</td>
<td>0.001-0.5</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucous Membrane</td>
<td>215</td>
<td>15</td>
<td>0.00015-96.4</td>
<td>1.0-96.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby Products</td>
<td>7</td>
<td>NR</td>
<td>0.000002-0.29</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
\(^a\) Includes products that can be sprays, but it is not known whether the reported uses are sprays
\(^b\) Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation
\(^c\) Includes products that can be powders, but it is not known whether the reported uses are powders
NR – no reported use
REFERENCES


Final Report on the Safety Assessment of Sodium Sulfate

Sodium Sulfate is used as a viscosity increasing agent in cosmetic formulations, at concentrations that are reportedly as high as 97%. No evidence of systemic toxicity was seen in oral exposure studies in animals, although there was moderate ocular irritation in rabbits when a granular sodium carbonate-Sodium Sulfate mixture was instilled. No developmental or reproductive toxicity was reported in rats or mice; there was an increase in birth weight in the mice. Sodium Sulfate was negative in mutagenesis assays. In several studies in which Sodium Sulfate was given with other agents, the results depended on the carcinogenicity of the other agents. Clinical data indicated no significant adverse effects following dermal, oral, or inhalation exposure. Because some irritation was seen under patch test conditions, it was concluded that the concentration should be limited to a level known to produce only a very small frequency of irritation if used in a leave-on application. Accordingly, Sodium Sulfate was found to be safe for use in rinse-off formulations, and safe at concentrations up to 1% in leave-on formulations.

INTRODUCTION
The following is a compilation of studies concerning the testing of Sodium Sulfate (CAS No. 7727-73-3 for the decahydrate form and 7757-82-6 for the anhydrous form).

A comprehensive review of literature published from 1920 to 1972 concerning sulfates (Franklin Institute Research Laboratories 1973) is available through the National Technical Information Service (NTIS). The review had been used by the Select Committee on Generally Recognized as Safe (GRAS) Substances in affirming the status of Sodium Sulfate (as well as other sulfates) as a GRAS compound (FDA 1978).

CHEMISTRY
Definition and Structure
Sodium Sulfate (anhydrous) is the inorganic salt with the chemical formula Na2SO4 (USP 1995). The empirical formula for Sodium Sulfate in the International Cosmetic Ingredient Dictionary and Handbook is H2SOa.2Na (Wenninger, Canterbery, and McEwen 2000). The decahydrate form has the chemical formula Na2SO4.10H2O.

Synonyms include: disodium sulfate; sulfuric acid, disodium salt (Wenninger, Canterbery, and McEwen 2000); Glauber’s salt (Taylor 1988); natriumsulfat; salt cake; sodium sulphate; thenardite; trona (RTECS 1995; Lewis 1993); bisodium sulfate; Caswell No. 793; and disodium monosulfate (Chemline 1995).

Physical and Chemical Properties
Some of the physical properties and chemical properties are listed in Table 1.

The decahydrate solution of Sodium Sulfate has a neutral pH (Budavari 1989). Sodium Sulfate reacts with aluminum, and emits toxic fumes of SOx and Na2O when heated to decomposition (Sax 1979; Lewis 1993).

CTFA lists the following specifications for cosmetic grade Sodium Sulfate (anhydrous): 3 ppm maximum Arsenic (as As) 20 ppm maximum Lead (as Pb), and 30 ppm maximum Selenium (as Se) (Nikitakis and McEwen 1990). The Sodium Sulfate sample must closely match the Cosmetic, Toiletry, and Fragrance Association (CTFA) Spectrum—IR with no indication of foreign materials (Nikitakis and McEwen 1990). These specifications are similar to those listed in the Food Chemicals Codex (FCC), except that the FCC restricts lead to a maximum of 10 ppm (National Academy of Sciences 1981).

Method of Manufacture
Sodium Sulfate occurs naturally as the minerals mirabilite and thenardite (Budavari 1989). It can also be prepared by the neutralization of sulfuric acid with sodium hydroxide (Rothschild 1990).

USE
Purpose in Cosmetics
Sodium Sulfate is used in cosmetic formulations as a viscosity increasing agent—aqueous (Wenninger, Canterbery, and McEwen 2000).

Scope and Extent of Use in Cosmetics
United States
As of January 1997, there were 28 reported uses of Sodium Sulfate in cosmetic formulations (FDA 1997). See Table 2. Concentrations of use are no longer reported to the FDA (1992). Data submitted to Cosmetic Ingredient Review (CIR) indicated that one company uses Sodium Sulfate at 0.5% in facial toner and lotion, 3.5% in liquid bubble bath, 82.0% in powder bubble bath, and 96.3% in bath powder (CTFA 1996a). Another company...
TABLE 1
Properties of Sodium Sulfate

<table>
<thead>
<tr>
<th>Property</th>
<th>Characteristic</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>142.04 Da (anhydrous)</td>
<td>Budavari 1989; Sax 1979; Lewis 1993a</td>
</tr>
<tr>
<td></td>
<td>322.20 Da (decahydrate)</td>
<td>Sax 1979</td>
</tr>
<tr>
<td>Appearance</td>
<td>White crystals or powder, odorless (anhydrous)</td>
<td>Sax 1979; Lewis 1993b</td>
</tr>
<tr>
<td>Melting point</td>
<td>888°C (anhydrous)</td>
<td>Sax 1979; Lewis 1993a</td>
</tr>
<tr>
<td></td>
<td>33°C (decahydrate)</td>
<td>Budavari 1989</td>
</tr>
<tr>
<td>Density</td>
<td>2.671 (anhydrous)</td>
<td>Sax 1979; Lewis 1993a</td>
</tr>
<tr>
<td></td>
<td>1.46 (decahydrate)</td>
<td></td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble: water, glycerin</td>
<td>Sax 1979; Lewis 1993a</td>
</tr>
<tr>
<td></td>
<td>Insoluble: alcohol</td>
<td></td>
</tr>
</tbody>
</table>

Reported use at 1% to 5% in liquid hand soap and body wash soap, and 0.1% to 1% in shampoos (CTFA 1996b).

**International**

Sodium Sulfate is listed in the Comprehensive Licensing Standards of Cosmetics by Category (CLS). Sodium Sulfate, which conforms to the specifications of the Japanese Standards of Food Additives and/or the Japanese Standards of Cosmetic Ingredients, has precedent for unrestricted use in all CLS cosmetic categories except eyeliners for which there has been no use precedence. Sodium Sulfate, anhydrous, which conforms to the standards of the Japanese Cosmetic Ingredient Codex has precedent for unrestricted use in all CLS categories except eyeliners and lip and oral preparations (Rempe and Santucci 1997).

**Table 2**

<table>
<thead>
<tr>
<th>Product category</th>
<th>No. formulations in category</th>
<th>No. containing Sodium Sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bath oil, tablets, and salts</td>
<td>117</td>
<td>1</td>
</tr>
<tr>
<td>Bubble baths</td>
<td>186</td>
<td>11</td>
</tr>
<tr>
<td>Bath soaps and detergents</td>
<td>341</td>
<td>1</td>
</tr>
<tr>
<td>Cleansing</td>
<td>630</td>
<td>2</td>
</tr>
<tr>
<td>Body and hand (excluding shaving)</td>
<td>776</td>
<td>3</td>
</tr>
<tr>
<td>Moisturizing</td>
<td>743</td>
<td>5</td>
</tr>
<tr>
<td>Night</td>
<td>185</td>
<td>1</td>
</tr>
<tr>
<td>Skin fresheners</td>
<td>181</td>
<td>1</td>
</tr>
<tr>
<td>Other skin care preparations</td>
<td>683</td>
<td>3</td>
</tr>
<tr>
<td><strong>1997 total</strong></td>
<td></td>
<td><strong>28</strong></td>
</tr>
</tbody>
</table>

In addition, Sodium Sulfate is recognized as a GRAS ingredient (FDA 1980; Rothschild 1990). Its use as a food additive is not restricted by the World Health Organization’s (WHO) Joint Expert Committee on Food Additives (JECFA), except that intake is limited by its laxative action (FAO/WHO 1994).

**General Biology**

**Absorption, Distribution, Metabolism, Excretion**

Human absorption, distribution, metabolism and excretion studies are reported in the Clinical Assessment of Safety section of this report.

**Oral**

Krijgsheld et al. (1979) used male Wistar rats (300–330 g body weight [bw]) to investigate the absorption of inorganic sulfate following oral administration of Na$_2$SO$_4$. One set of animals had a permanent catheter placed in the right atrium to collect blood samples. The samples were analyzed by liquid scintillation to determine plasma $^{35}$S concentrations. Groups of six animals were dosed under light anesthesia by gastric tube with 600 $\mu$Ci/kg bw Na$_2$SO$_4$ in 2 ml water. One group received only the tracer dose. Another two groups received, in addition to the tracer, either 1.0 or 5.0 mmol nonradioactive Na$_2$SO$_4$. Feed and water were provided ad libitum.

Radioactivity was detected in the plasma 15 minutes after administration of the tracer dose. A peak activity of >4000 cpm was reached 1.5 to 2 hours following administration. By 10 hours, 50% of the maximum plasma concentration remained; by 19 hours only 10% of the maximum plasma radioactivity remained. In animals that also received nonradioactive Sodium Sulfate, the peak radioactivity was again reached at 1.5 to 2 hours post administration. However, the amount of radioactivity in the plasma decreased as the dose of nonradioactive Sodium Sulfate increased, indicating that the "fractional absorption of (labeled) Sodium Sulfate decrease(d) as the administered dose increase(d)."

The urinary excretion of sodium sulfate was studied in a different group of rats (Krijgsheld et al. 1979). Animals were treated via a gastric tube with 50 $\mu$Ci/kg bw Na$_2$SO$_4$ in 2 ml water to which was added either varying amounts of sodium
Chloride or between 0.25 to 5.0 mmol nonradioactive Na₂SO₄. Control rats received water with sodium chloride added. The rats were placed in metabolic cages and urine was collected for as long as 7 days following oral sulfate administration. Rats that received the two high sulfate doses (2.5 and 5.0 mmol) developed diarrhea that started 4 hours after administration and lasted for 4 hours; removal of the feces thus resulted in some loss of Na₂SO₄ and were analyzed for sulfate concentration.

When the radioactive Sodium Sulfate was administered with either saline or the two lowest doses of nonradioactive Sodium Sulfate (0.25 or 0.5 mmol), about 90% of the administered dose was recovered in the urine within 24 hours. (The researchers attributed the remaining 10% to incorporation into unidentified macromolecules in the body.) When the amount of nonradioactive Sodium Sulfate was increased to 1.0, 2.5, and 5.0 mmol/rat, the percentage of radioactivity recovered in the 24-hour urine decreased to 73%, 57%, and 56%, respectively. Serum sulfate concentrations of 1.34, 1.95 and 2.13 mmol/L were found in blood samples from animals dosed with 0.5, 2.5, or 5.0 mmol nonradioactive Sodium Sulfate, respectively. Correspondingly untreated controls had serum sulfate concentrations of 0.77 mmol/L, whereas those animals treated with varying amounts of sodium chloride and water (vehicle control) had concentrations between 0.57 and 0.66 mmol/L.

Its detection in the plasma soon after administration and the urinary excretion of 90% of the administered radioactivity within 24 hours (when low doses of nonradioactive sulfate were also added), indicating almost complete absorption of the dose from the gut. The researchers considered that orally administered Sodium Sulfate was rapidly absorbed in rats.

The results of Krijgsheld et al. (1979) corroborated those reported by Hwang (1966) in which 57% to 74% of an orally administered dose of 2800 mg/kg Na₂³⁵SO₄ was recovered in the 24-hour urine of four rats.

**Parenteral**

Dziewiatkowski (1949) conducted a study in which 1 mg Na₂³⁵SO₄ was administered intraperitoneally (IP) to 14 male and 13 female adult rats (180–330 g). Animals were killed at various times postdosing and tissue samples were collected. Approximately 67% of the administered ³⁵S was excreted in the urine within 24 hours. By 120 hours, 85% was recovered in the urine; when fecal excretion was included, 95% of the administered dose had been recovered. Rapid elimination was noted in the blood, liver, and brain with almost complete elimination by 48 hours. However, a notable rise in the ³⁵S concentration was noted at 8 hours in bone and at 24 hours in bone marrow. Elimination was slow in these two tissue samples with significant concentrations noted 120 hours after administration.

Odeblad and Boström (1952) used autoradiography to measure the incorporation of ³⁵S Sodium Sulfate into different organs of rats and rabbits. Five adult rats (200 g) received subcutaneous (SC) injections of 100 μCi ³⁵S as “carrier free” Na₂SO₄ diluted with 0.1 mg nonradioactive Na₂SO₄ in 0.2 ml distilled water/100 g bw. One adult rabbit was injected with 2.0 mCi ³⁵S as Na₂SO₄ in 4 ml of distilled water, containing 0.2 mg carrier. All animals were killed 48 hours after dosing and various organs were removed. In rats, “very large amounts” of radioactivity were detected in the epithelium of the esophagus and ileum, in the cornea, and in the cartilage of the trachea. In the rabbit, “large amounts” of radioactivity were detected in the tunica intima and tunica media of the aorta, and in the respiratory epithelium and cartilage plates of the lungs. The researchers considered ³⁵S to be taken up by tissues where sulforhodopsin is present.

Boström and Aqvist (1952) reported that Na₂³⁵SO₄ administered IP to rats was incorporated in small amounts into the chondroitin sulfate acid of the costal cartilage within 24 hours, and in trace amounts into taurine isolated from the liver within 8 hours. The researchers reported that the exogenous sulfate was not incorporated into methionine or cysteine. Exogenous sulfate was taken up primarily into mucopolysaccharides.

In a study by Dohlmann (1957), Na₂³⁵SO₄ was administered intravenously (IV) to rabbits which were then killed at various times postdosing; eyeballs were enucleated and analyzed for radioactive sulfur content. The radioactive sulfur was rapidly taken up by the eyeball with high concentrations being detected in the uvea. Turnover rates were also high in the uvea but slow in the cornea and lens. By day 3 after dosing, concentrations remained high in the inner layers of the cornea and sclera but were low in the uvea, retina, and the pia and dura of the optic nerve head. No radioactivity was detected within the aqueous humor or vitreous body.

Na₂³⁵SO₄ was injected into the femoral artery of a dog (Balchum, Dybicki, and Meneely 1960). After 100 minutes, 0.6% was retained in the trachea, 0.2% in the lungs, 4.6% in the liver, 0.26% in the spleen, 0.3% in the kidneys, and 0.6% in the brain.

**Effects on Enzymes and Serum Parameters**

Intravenous injection of Sodium Sulfate at <400 mg/L of blood into a 15-kg dog increased biliary volume and biliary salt excretion twofold (Chabrol and Maximin 1929).

Sodium Sulfate injected intravenously at 175 mg/kg into a rabbit produced a 22% drop in serum calcium concentrations in 4 hours. Inorganic phosphorus concentrations were decreased by 34% at 1.75 hours, but returned to normal at 4 hours. No changes were noted in the serum magnesium concentration (Brookfield 1934).

Fasted and fed female Golden labradors were infused with 3 parts of 5% creatinine and 2 parts of Sodium Sulfate (50 mM) at rates of 0.75 and 1.0 ml/min. The glomerular filtration rate was increased by 30% to 50% over initial values in fasted dogs. Sodium Sulfate administration increased the phosphate-filtered...
load as measured from heparinized plasma; this effect was not noted when 5% creatinine alone was administered (Fouks 1955).

Kowarski, Kowarski, and Berman (1961) demonstrated that the addition of 1% Sodium Sulfate to milk fed to rats decreased calcium ionization and reduced calcium absorption from the gut. Calcium retention was reduced by 50%.

Duhm, Deuticke, and Gerlach (1969) reported that the addition of Sulfate to cultures of human erythrocytes in plasma inhibited, by almost 80%, the spontaneous degradation of 2,3-diphosphoglycerate. This effect of Sulfate was also noted in erythrocytes incubated in glucose-free media and in hemolysates under conditions in which no synthesis of 2,3-diphosphoglycerate occurred. High 2,3-diphosphoglycerate concentrations in vivo reduced the affinity of hemoglobin for oxygen and thus favored the release of oxygen in tissues.

Drug Interaction

Acetaminophen

Slattery and Levy (1977) reported that Sodium Sulfate increased the LD_{50} of IP acetaminophen in Swiss mice from 425 to 575 mg/kg. Groups of 10 mice (25-30 g) had received single IP injections of 300 to 800 mg/kg acetaminophen together with an equimolar amount of Sodium Sulfate. (Control groups received acetaminophen with varying amounts of sodium chloride.)

In a follow-up study using Sprague-Dawley rats, Galinsky, Slattery, and Levy (1979) demonstrated that plasma acetaminophen concentrations decreased and plasma acetaminophen sulfate concentrations increased more rapidly in Sodium Sulfate-treated rats as compared to controls that were given an identical amount of sodium in the form of sodium chloride. The researchers considered that the decreased acetaminophen toxicity caused by Sodium Sulfate dosing was due to accelerated elimination of acetaminophen. Similarly, Lin and Levy (1986) reported that concomitant administration of inorganic sulfate (delivered as Sodium Sulfate) to Sprague-Dawley rats increased by 1.5-fold the total clearance of large doses of acetaminophen (300 mg/kg), and increased by twofold the fraction of that dose eliminated as acetaminophen sulfate, when compared to rats that had not received supplemental sulfate. Clearance was limited by the activity of sulfotransferase enzymes that are responsible for acetaminophen sulfate formation.

Subsequent studies by Hjelle, Brzeznicka, and Klaassen (1986) using adult male CF-1 mice found that administration of either Sodium Sulfate (4 mmol/kg) or N-acetylcysteine (NAC) increased serum sulfate and hepatic adenosine 3'-phosphosulfate 5'-phosphosulfate concentrations. The mice (23-32 g) received IP doses of 400 or 600 mg/kg acetaminophen (2.5 and 4 mmol/kg) dissolved in either Sodium Sulfate or NAC vehicle. No significant change in acetaminophen sulfation or elimination was noted with administration of NAC or Sodium Sulfate. However, unlike NAC, Sodium Sulfate did not attenuate the marked decrease in glutathione in the liver observed after acetaminophen administration. Also, NAC decreased covalent binding of tritium derived from [3H]acetaminophen to liver protein. Sodium Sulfate did not. Sodium Sulfate did not protect against acetaminophen-induced hepatotoxicity whereas lethality was reduced in NAC-treated animals.

Selenium

Groups of five weanling Sprague-Dawley rats were fed diets containing 500 and 1000 mg Sodium Sulfate/kg feed in conjunction with 5, 10, and 20 mg Se/kg feed. Mortality was 60% and 100% in mice treated with 10 and 20 mg selenium, respectively, regardless of the Sodium Sulfate dosage; no deaths were found in the 0 and 5 mg selenium groups. The concurrent treatment with Sodium Sulfate did not significantly alter the course of selenium toxicity (i.e., feed intake, daily weight gain, testis weight, hepatic hemorrhage and necrosis, renal necrosis, arrested spermatogenesis). The main effect of the SO_{4} was increased liver copper concentrations (Kezhou et al. 1987).

Effect on DDT Absorption

A group of six male Sprague-Dawley rats (230–330 g) was treated via feeding tube with 80 mg/kg ^{14}C-DDT in a volume of 10 ml/kg of cathartic (15% Sodium Sulfate containing 20% acacia). One hour later each rat received a second dose of the Sodium Sulfate cathartic without DDT at the rate of 10 ml/kg. A second dose of DDT with cathartic was given after 24 hours. A control group of rats was treated with distilled water containing 20% acacia. Feces and urine were collected during the experiment and analyzed for radioactivity by liquid scintillation. Rats were killed 24 hours after the second dose of DDT. Perirenal and peritesticular adipose tissue samples were collected and analyzed by gas chromatography. Although the difference was not of statistical significance, all Sodium Sulfate–treated rats had adipose DDT concentrations (95 ppm) below the control group (137 ppm). Once the values were corrected for contamination of urine with loose feces (resulting from Sodium Sulfate treatment), the liquid scintillation values corresponded with the adipose tissue measurements. It was estimated that 60.8% of the administered DDT was recovered in the feces of the Sodium Sulfate group rats versus 57.5% for the control rats (Keller and Yeary 1980).

ANIMAL TOXICOLOGY

Short-Term Oral Toxicity

A group of six weanling male Sprague-Dawley rats fed either 0.88, 8.64, or 138 mmol Sodium Sulfate/kg basal diet for up to 4 weeks had no significant differences in weight gain, feed intake, feed-gain ratio, or water intake as compared to control rats. Hemoglobin, red blood cell count, white blood cell count, serum protein, alkaline phosphatase, and inorganic phosphate concentrations were also comparable to values for the control group. No changes were observed in gastrointestinal organ weights or...
in the length or color of the small intestine (Moinuddin and Lee 1960).

**Acute Inhalation Toxicity**

Amduer et al. (1978) found no adverse pulmonary effects in 10 guinea pigs exposed for 1 hour to 0.90 mg/m³ Sodium Sulfate (particle size 0.1 μm). No change in resistance was noted. A slight decrease in compliance was observed; it was not statistically significant. Sodium Sulfate was the least irritating of the sulfate aerosols tested (ranked in decreasing order: ammonium sulfate > ammonium bisulfate > copper sulfate > sodium sulfate).

Sackner et al. (1981) performed a variety of studies to investigate the effects of sulfate aerosols on cardiopulmonary function in dogs and tracheal mucous velocity of sheep. In the studies described below, statistical analysis compared the response to sulfates against the response to sodium chloride (control).

In a brief exposure study, five intubated anesthetized dogs breathed aerosol generated from a 0.1% Sodium Sulfate solution (particle size 0.1-0.2 μm) for 7.5 minutes. The aerosol generated had a mass concentration of 1.0 mg/m³. Measurements of lung volume and mechanics were made before exposure and at 5, 15, 30, 60, 120, and 180 minutes after exposure termination. After completion of the final measurements, the animals were exposed for 7.5 minutes to aerosol generated from a 1.0% Sodium Sulfate solution (particle size 0.1-0.2 μm). This aerosol had a mass concentration of 8.0 mg/m³. Lung mechanics measurements were made at 5, 15, and 30 minutes following termination of the second exposure. No significant alterations in total respiratory resistance, static lung compliance, functional residual capacity, specific total respiratory conductance, and specific lung compliance were noted in the animals exposed to Sodium Sulfate.

In an intermediate exposure study, five intubated anesthetized dogs breathed aerosols generated from 0.5% Sodium Sulfate solution for 4 hours. The aerosol had a mass concentration of 5.0 mg/m³. Measurements of lung volume, breathing mechanics, and hemodynamics were made before, hourly during, and for 2 hours after exposure. "No significant alterations" were noted (Sackner et al. 1981).

In a study by Schlesinger (1984) comparing the irritancy potential of inhaled sulfate aerosols, the following ranking was determined: sulfuric acid > ammonium bisulfate > ammonium sulfate, (equivocal to) Sodium Sulfate. Five rabbits had been exposed for 1 hour to a maximum concentration of almost 2000 μg/m³ Sodium Sulfate aerosol and measurements were made of bronchial mucociliary clearance. No significant adverse effects were reported.

**Acute Parenteral Toxicity**

In addition to the inhalation studies described in the earlier section, Sackner et al. (1981) also performed intravenous studies in which anesthetized dogs were injected with 1 mg of Sodium Sulfate in 10 ml sterile water. Measurements of breathing mechanics, functional residual capacity, pulmonary and carotid arterial pressures, cardiac output and arterial blood gases were done at 15, 30, 45, and 60 minutes following the IV injection. After the final measurement was taken, 10 mg Sodium Sulfate in 10 ml water was injected and the same parameters at the same time intervals were measured again. A nondonose dependent alteration in pulmonary function was noted. Specifically, 10 mg Sodium Sulfate, "produced a maximal fall in specific lung compliance of 11% 15 minutes after injection (p < .05)". This effect was not noted with either the 1 or 100 mg dose. The 10 mg dose of Sodium Sulfate also produced a, "rise in cardiac output of 11% at 60 minutes and a maximum increase of stroke volume of 22% at 45 minutes after injection (p < .05)." No significant hemodynamic changes resulted from the 1 or 100 mg dose.

**Ocular Irritation/Toxicity**

Griffith et al. (1980) classified a sodium carbonate–Sodium Sulfate granular mixture (1:1 w/w) as causing moderate ocular irritation. The test material was applied directly to one cornea of three albino rabbits at volumes of 0.01, 0.03, and 0.1 ml. Irritation was graded on days 1, 2, 3, 4, 7, and 14 following treatment. The reactions were scored using the Draize scale that allows a maximum score of 110. The average maximum scores noted were 11, 17, and 36 for the 0.01, 0.03, and 0.1 ml doses, respectively. These reactions took between 4 and 21 days to return to normal.

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

**Oral**

In validation of an in vivo developmental toxicity screen, Seidenberg, Anderson, and Becker (1986) administered various chemicals to pregnant ICR/SIM mice (32-36 g) by oral intubation on days 8 through 12 of gestation. Sodium Sulfate, 2,800 mg/kg/day, was administered in a water vehicle to 28 mice. Animals were housed individually; feed and water were available ad libitum. Mice were weighed on days 7 and 13 to
determine maternal weight gain. The dams were allowed to deliver and neonates were examined, counted, and weighed on the day of birth and day 3. No maternal toxicity was observed in the Sodium Sulfate dose group; average weight gain was 8.6 g (compared to 8.5 g for nontreated controls that had received water via intubation). The Sodium Sulfate group had 24 litters with no resorptions (control had 25 with no resorptions). Survival of neonates was 100% between days 1 and 3 in the Sodium Sulfate group. The average neonatal weight at birth for the Sodium Sulfate group was 2.58 g compared to 2.42 g for control neonates.

In a subsequent publication discussing the validity of the above described developmental screen, Seidenberg and Becker (1987) considered the slight but significant increase in neonatal body weight on day 1 to be a positive result for Sodium Sulfate. However, in outlining the protocol for the screen, it was stressed that "overt maternal toxicity is required"; such a dose was not reached in the Sodium Sulfate group. The researchers admitted, "a teratogen may produce a positive response in the developmental toxicity screen without inducing overt toxicity in dams." However, noting the lack of published teratogenic data via the oral route for Sodium Sulfate, the researchers were unable to interpret whether the results were valid or a false positive.

Parenteral

Sodium Sulfate induced a low incidence (6%) of skeletal anomalies in mice when injected subcutaneously on a single day of gestation (Arcuri and Gautieri, 1973).

Knight, Van Wart, and Roe (1978) studied the effects of salicylamide on the sequential uptake and loss of radioisulfate by maternal and fetal rat tissue. On day 17 of gestation, a control group of 24 pregnant Holtzman rats (230–250 g), maintained since gestation day 6 on a 25% casein diet, was injected intramuscularly with Na235SO4 at a dose of 25 μCi/100 g bw (Na235SO4 in water, 100 μCi/ml). The experimental groups, which had been maintained on casein diets supplemented with varying amounts of salicylamide, also received an injection of Sodium Sulfate on day 17. Dams were killed sequentially at intervals up to 24 hours postinjection. A blood sample was obtained at the time of killing, the maternal liver was extracted, and fetuses were grossly examined. Homogenates of each fetus and placenta, as well as maternal liver and serum, were analyzed by a scintillation counter. No malformations were noted in any of the 108 fetuses of the control group; there were six resorptions in control rats, the uptake and retention of radioisulfate per unit weight of placenta or per placenta varied inversely with the number of placentas per dam or the placental weight. Uptake by the fetus was maximal after 2 hours, followed by a rapid decline in the following hour; the loss rate was slow. Uptake by the fetus was significantly correlated with maternal serum concentrations.

GENOTOXICITY

Sodium Sulfate at concentrations up to 275 μg/well was negative in the microscreen assay (Rossman et al. 1991). The assay measures prophage induction into Escherichia coli as an indicator of DNA damage to the bacteria.

Sodium Sulfate was among several salts tested for enhanced transformation of Syrian hamster embryo cells (HCE) by a simian adenovirus, SA7. A concentration of 7.0 mM Sodium Sulfate produced an enhancement 1.2 times that of the untreated control. (The enhancement was expressed as the ratio between the transforming frequency of treated, surviving cells and the transforming frequency of control cells.) The results for Sodium Sulfate were considered negative as a concentration >0.9 mM was necessary to produce the effect (Casto, Meyers, and Dipaolo 1979).

COCARCINOGENICITY

Yamamoto et al. (1973) explored whether supplemental administration of Sodium Sulfate would restore the cocarcinogenicity of N-hydroxy-N-2-fluorenylacetamide (N-OH-FAA) despite the presence of the inhibitor p-hydroxyacetanilide. Groups of rats were maintained for 16 weeks on feed containing: (1) 0.0213% (0.89 mmole/kg) N-OH-FAA; (2) carcinogen plus 0.89% (59 mmole/kg) p-hydroxyacetanilide (a 66 molar excess); or (3) carcinogen plus inhibitor plus 2.52% (178 mmole/kg, 3 molar equivalents) Sodium Sulfate. Following dosing, animals were maintained on untreated feed for an additional 10 weeks. Animals were killed at the end of the experiment and necropsy performed. Three animals from each group were housed in metabolism cages; urine was collected separately over a 24-hour period and analyzed for inorganic sulfate. Hepatomas were observed in all 10 animals of group 1, in four of the 20 rats of group 2, and in none of the 20 animals of group 3. Further, hyperplastic nodules were neither observed in four animals from group 2 nor in 11 animals from group 3. Sodium Sulfate appeared to inhibit the cocarcinogenicity of N-OH-FAA or increase the inhibitory affect of p-hydroxyacetanilide.

A second experiment was conducted by Yamamoto et al. (1973) using a higher dose (0.032%, 1.34 mmole/kg) of N-OH-FAA as well as one-third the Sodium Sulfate amount of the above described study (0.84%, 59 mmole/kg, 1 molar equivalent). Again rats were maintained for 16 weeks on treated feed followed, this time, by an additional 16 weeks on control feed. Hepatomas were noted in all 5 animals that received the carcinogen alone, in 6 of 12 animals that received the carcinogen plus inhibitor, in 5 of 6 animals that received the carcinogen, inhibitor, and 1 equivalent of dietary Sodium Sulfate, and in 4 of 12 animals that received the carcinogen, inhibitor plus 3 equivalents of Sodium Sulfate. With the greater amount of carcinogen used in this second study, Sodium Sulfate had no additional effect on the actions of p-hydroxyacetanilide.

Animals that received the carcinogen alone excreted free sulfate in the urine, whereas in animals that also received p-hydroxyacetanilide the sulfate was mostly conjugated. Groups
that also received 1 or 3 equivalents of Sodium Sulfate had greater concentrations of total and free urinary sulfate (Yamamoto et al. 1973).

Blunk and Crowther (1975) studied the Sodium Sulfate activation of the carcinogen (and azo dye) 3'-methyl-4-dimethylaminoazobenzene (MeDAB). Groups of 15 male Sprague-Dawley rats were fed for 16 weeks diets containing either 0.06% MeDAB or 0.06% MeDAB plus 0.84% Sodium Sulfate. Another group of five rats received feed containing only 0.84% Sodium Sulfate. The amount of feed available was restricted to that of the cage of five rats received feed containing only 0.84% Sodium Sulfate. The only exception was that leukemia (in 1 of 19 animals) was noted after an 18-week latent period (Cohen and Bryan 1978).

Samelson, Nelson, and Nyhus (1985) reported that Sprague-Dawley rats with acid stool pH, produced by consumption of Sodium Sulfate had significantly (p < .05) fewer colon tumors than DMH alone. A group of 33 rats was fed a diet supplemented with 50 mg Sodium Sulfate/20 g pellet. After 4 weeks of this diet, no tumors were observed in all rats for 16 weeks. Animals were killed in 8 weeks after the last injection. The final number of colon tumors was as follows: no tumors in the untreated control group; 77 tumors in the group receiving Sodium Sulfate alone; and, 73 tumors in the group receiving Sodium Sulfate and DMH. A mean score of 3.5 tumors/rat was observed for the DMH-alone group and a mean of 2.3 tumors/rat was found for the Sodium Sulfate plus DMH group.

CLINICAL ASSESSMENT OF SAFETY

Absorption, Distribution, Metabolism, Excretion Oral

Cocchetto and Levy (1981) investigated absorption of Sodium Sulfate in humans as measured by recovery of free sulfur in the urine. Five healthy males (66–79 kg bw) were orally dosed with 18.1 g of decahydrate Sodium Sulfate (56.3 mmol, equivalent to 8.0 g of the anhydrous salt), in either a single dose or four equally divided hourly doses. The Sodium Sulfate was dissolved in 50 ml of warm water and ingested during a low-fat breakfast. With a minimum of 1 week between treatments, the dosing protocol was repeated but reversed and those who had previously received a single dose now received the divided doses and vice versa. Urine was collected over 0 to 24, 24 to 48, and 48 to 72 hour periods. All subjects experienced severe diarrhea following the single dose of Sodium Sulfate, starting 2 hours following ingestion and lasting up to 24 hours. Panelists who received divided dosings experienced mild to no diarrhea.

The baseline individual average excretion rate of inorganic sulfate (determined by collection of three 24-hour urine samples prior to sulfate treatment) ranged from 13 to 25 mmol/24 h with the two individuals with the lowest body weights having the lowest baseline values. Although the baseline excretion of free sulfate was unaffected by changes in urine flow rate, the baseline excretion rate of total sulfate (including organically bound sulfate) increased almost linearly with increasing flow rate. This effect was also observed following sulfate administration.
Following Sodium Sulfate administration, the cumulative amounts of free sulfate excreted in the 24-, 48-, and 72-hour urine were significantly greater than the amount of free sulfate excreted in the same time periods in control experiments \((p < .01)\). On average, 24 hours postdosing, 36.4% of the sulfate administered in a single dose (standard deviation [SD] 15.4%) and 43.5% of the divided dose (SD 12.0%) had been recovered. By 48 hours, an average of 49.5% of the single (SD 15.6%) and 53.1% of the divided dose (SD 7.5%) had been recovered. And by 72 hours, 53.4% of the sulfate administered in the single dose (SD 15.8%) and 61.8% administered in the divided dose (SD 7.8%) was recovered. The researchers noted "considerably less inter-individual variation" in urinary recovery of free sulfate following the divided dose.

A subsequent study by Morris and Levy (1983) in which eight panelists (six males, two females) ingested 9 g Sodium Sulfate (decahydrate) within a 1-hour period resulted in increased serum inorganic sulfate concentrations. The mean values were 0.410 mM prior to Sodium Sulfate intake, and 0.513 mM following ingestion of the test material \((p < .001)\). Urinary excretion of inorganic sulfate also increased after ingestion of Sodium Sulfate. The renal clearance of endogenous creatinine was not affected.

**Intravenous**

Six normal human panelists received a 1-L infusion of 4% Sodium Sulfate, resulting in a decrease of urinary pH from 6.05 to 4.32 with a doubling of ammonia and titratable acid excretion. In 10 patients with renal disease and normal serum bicarbonate concentrations (>25.1 meq/L), the infusion resulted in a rise of urine pH without a change in ammonia or titratable acid excretion. Therefore, net acid excretion fell. In the same 10 patients with renal disease but with serum bicarbonate concentrations below 20 meq/L, the Sodium Sulfate infusion produced results similar to those in the six normal patients (Seldin et al. 1967).

Six males (aged 55–70 years) with normal renal function received an IV dose of 1.1 Mbp (30 μCi) radioactive Sodium Sulfate and collected urine for 72 hours. By 24 hours, 88% of the Na₂³⁵SO₄ dose was excreted in the urine; 87% was excreted by 72 hours. Heparinized blood samples were collected from another two panelists (one of each sex) every minute for the first 15 minutes after injection, and then every 15 minutes until 3 hours following injection. By extrapolating the early phase of the plasma disappearance curve, the researchers predicted that 1% to 2% of the administered Sodium Sulfate remained in the plasma 24 hours after injection (Burke and Staddon 1983).

**Effect on Drug Absorption**

**Acetaminophen**

Eight healthy adults received on separate occasions, 1 g acetaminophen; 1 g acetaminophen and 18 g Sodium Sulfate (decahydrate); 1 g acetaminophen and 10 g activated charcoal; and 1 g acetaminophen and 10 g activated charcoal and 18 g Sodium Sulfate, in random order. The Sodium Sulfate was administered such that at zero time, 4.5 g Sodium Sulfate USP was ingested in 50 ml water, followed by 4.5 g in 100 ml water at 2, 4, and 6 hours. Urine was collected for 48 hours and analyzed for acetaminophen, its metabolites, and inorganic sulfate. The panelists tolerated the various treatments well, except for instances of loose stools following Sodium Sulfate ingestion. Sodium Sulfate did not interfere with the absorption of acetaminophen by charcoal and, likewise, charcoal did not affect the absorption of Sodium Sulfate. Sodium Sulfate did not increase the formation of acetaminophen sulfate. This finding was consistent with expectations as the researchers noted administration of inorganic sulfate increases acetaminophen sulfation only when endogenous sulfate supplies are markedly depleted (i.e., very large doses of acetaminophen would be needed). The researchers considered that a combination of activated charcoal and Sodium Sulfate can be useful in the treatment of acetaminophen overdose (Galinsky and Levy 1984).

**Other Drugs**

Mattila, Takki, and Jussila (1974) reported that ingestion of 20 g Sodium Sulfate as two 10-g doses, 30 minutes apart resulted in diarrhea in 11 healthy panelists. Isoniazid (INH) was given with the first dose and sulfafurazole and acetylsalicylic acid were given with the second dose. Blood samples were taken at 30 minutes after the first dose (just prior to ingestion of the second dose) and at 30, 60, 120, and 240 minutes following the second dose. A control study had been conducted 3 days prior in which the drugs were administered following the same protocol but without Sodium Sulfate. Sodium Sulfate reduced serum concentrations and urinary excretion of INH and reduced the absorption rate and urinary excretion of sulfafurazole. The absorption of acetylsalicylic acid from a slow-release tablet was unaffected. The absorption of acetylsalicylic acid was slightly reduced in seven panelists when a single dose of Sodium Sulfate was administered.

Campbell et al. (1985) studied the effect(s) of Sodium Sulfate ingestion on methyl dopa metabolism. Twenty-four panelists were randomized to ingest either 13.24 mg/kg Sodium Sulfate with 3.5 mg/kg methyl dopa powder or methyl dopa alone. One week later, the subjects were given the alternate treatment. Urine was collected for 24 hours following dosing. Sodium Sulfate ingestion increased the concentration of methyl dopa sulfate (from 50.1% to 66.0%) and decreased the concentration of free methyl dopa (from 27.3% to 17.1%) in the urine. A positive correlation \((r = .545, p < .01)\) between platelet phenol sulfotransferase (PST) activity and the percentage of drug excreted as methyl dopa sulfate was noted with concurrent intake of methyl dopa and Sodium Sulfate. This relationship was not noted when methyl dopa was taken alone \((r = -.340, p > .10)\). PST catalyzes the metabolism of methyl dopa sulfation; 3'-phosphoadenosine-5'-phosphosulfate (PAPS) serves as the sulfite donor for the PST reaction. No gastrointestinal problems associated with Sodium Sulfate ingestion were noted.
**Oral Toxicity**

In a study to determine the role of fecal pH on the risk of colon cancer, 27 patients with a history of colonic polyps received a mean dose of 4 g/day of Sodium Sulfate for 14 days (Kashtan et al. 1990). A control group of 25 patients received placebo. The panelists were instructed to self-adjust the daily dose (not to exceed 6 g/day) such that two to three soft stools were produced each day. No adverse effects were noted.

**Inhalation Toxicity**

Sackner, Ford, and Kim (1979) exposed for 10 minutes five healthy and five asthmatic adults to 1, 2, and 3 mg/m³ Sodium Sulfate aerosol with a mass median aerodynamic diameter (MMAD) of 0.5 μm. Respiratory parameters were measured for up to 1 hour following exposure. Mean values for the measured respiratory parameters were similar to the values obtained for exposure to equivalent amounts of sodium chloride (control). Two asthmatics had a 15% to 20% fall in forced exhalation volume (FEV₁); however, the response did not worsen with exposure to higher concentrations. In a subsequent experiment, six normal and six asthmatic adults were exposed for 10 minutes to 3 mg/m³ Sodium Sulfate aerosol. Lung function measurements were made for 3 hours following exposure. Again, mean values for Sodium Sulfate when compared to sodium chloride indicated no adverse effect on pulmonary function. An immediate 15% to 20% fall in FEV₁ was noted in two of six asthmatics after breathing either Sodium Sulfate or sodium chloride.

Kelada and Elinton (1978) found no abnormality attributable to long-term occupational exposure to Sodium Sulfate dust in 119 workers from five sodium sulfate surface solution mines. Dust exposure concentrations ranged from <5 mg/m³, 40 mg/m³ in the main plant, and up to 150 mg/m³ during loading of the final product. The workers had between 2 months to 31 years of exposure. The workers were not distinguishable from the general population with regards to parameters measured in the cardiorespiratory, gastrointestinal, or hepatorenal systems. Lung function, serum sulfate, calcium and electrolytes were within normal limits. There were no significant differences in the serum sulfate concentrations of workers with > 10 years experience as compared to those from workers with <10 years experience.

**Dermal Sensitization**

An effective Sodium Sulfate concentration of 1.01% (1.25% aqueous solution of a bubble bath containing 80.8% Sodium Sulfate) was tested in a repeated insult patch test on 61 panelists. The concentration tested was a 100-fold exaggeration of normal use levels. The first induction patch was left in place on the back for 48 hours and the remaining eight patches were applied for 24 hours of exposure. Every third patch (i.e., patches 1, 4, 7 and 2, 5, 8) was applied to the same site on the back. Following a 3-week nontreatment period, panelists were challenged on a previously unexposed site with a 48-hour patch. One panelist had a single incidence of mild erythema after exposure to induction patch 4. No reactions were observed at challenge (CTFA 1976).

**Summary**

Sodium Sulfate is a GRAS ingredient that is used in cosmetic formulations as a viscosity increasing agent. In 1997 there were 28 reported cosmetic uses. Data from two sources indicated use at a variety of concentrations, with a maximum use of almost 97% in bath formulations. Sodium Sulfate is rapidly absorbed and excreted following oral intake.

No significant adverse effects were noted in rats following short-term oral dosing or in anesthetized dogs or conscious sheep following brief or intermediate inhalation exposures. A granular
sodium carbonate–Sodium Sulfate mixture produced moderate ocular irritation in rabbits.

No developmental changes were noted in rat fetuses whose dams had received an intramuscular injection of Sodium Sulfate on gestation day 17. An oral-dose study found increased neonate birth weight in fetuses of mice which had received Sodium Sulfate during gestation.

Sodium Sulfate was negative in mutagenicity assays. Results of various oral cocarcinogenicity assays were dependent on the carcinogen administered with Sodium Sulfate (and an inhibitor).

Clinical studies reported no significant adverse effects following oral or inhalation exposure to Sodium Sulfate. Mild-to-no irritation and no sensitization were noted in dermal studies that tested Sodium Sulfate–containing bath formulations at exaggerated-use concentrations and conditions.

**DISCUSSION**

In assessing the safety of Sodium Sulfate, the CIR Expert Panel relied on its GRAS status to preclude the need for many studies. Further, the submission of clinical dermal irritation and sensitization data by the cosmetics industry addressed the Panel’s concerns about the lack of such studies in the published literature. The submitted data showed Sodium Sulfate induced no-to-mild irritation and no sensitization when tested in bath formulations. The Panel decided that these data were sufficient to conclude that Sodium Sulfate was safe as used in rinse-off formulations.

However, because some of these formulations produced irritation under patch test conditions, the Panel restricted the use of Sodium Sulfate in leave-on products. Results from a clinical sensitization study were considered particularly useful because the testing protocol specified repeated prolonged exposure. An induction period in which nine 24-hour insult patches containing 1.01% Sodium Sulfate were applied noted one isolated incidence of mild erythema in 1 of 61 panelists. The Panel rounded the figure to 1% to arrive at the limit for use in leave-on products.

**CONCLUSION**

Based on the available data, the CIR Expert panel concludes Sodium Sulfate to be safe as used in rinse-off formulations, and safe up to 1% in leave-on formulations.

**REFERENCES**


CTFA. 1985. Human patch test: Sodium Sulfate. Submission of unpublished data by CTFA. Received June 19, 1996. (1 page.)


CTFA. 1996a. Use levels for various ingredients. Submission of unpublished data by CTFA. Received September 5, 1996. (1 page concerning Sodium Sulfate.)

CTFA. 1996b. Concentration of Sodium Sulfate in Company products. Submission of unpublished data by CTFA. Received September 24, 1996. (1 page.)


2 Available for review: Director, Cosmetic Ingredient Review, 1101 17th St., NW, Suite 310, Washington, DC 20036-4702, USA.
SODIUM SULFATE


VCRP Data For Sodium Sulfate-2016

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VCRP Data For Sodium Sulfate-2016 (con't)

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)
FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel
DATE: March 24, 2016
SUBJECT: Comments on the Re-review: Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics (prepared for the March 31-April 1, 2016 CIR Expert Panel meeting)

Key Issue
If the CIR Expert Panel decides to open this report, Calcium Sulfate (321 uses reported to the VCRP - which is a similar number of uses as ingredients under consideration for the 2017 priority list) and Potassium Sulfate (67 uses reported to the VCRP) should be added to this report. Calcium and Potassium Sulfates have not yet been included in a concentration of use survey.

Additional Considerations
Memo, Cosmetic Use, Summary - Saying the use data in the original report were not “comprehensive” suggests that the current use information is comprehensive. The current use information is representative. It would be more appropriate to call the use information in the original report “limited”.

Cosmetic Use - What were the types of hair preparations for which there were 4 reported uses to the VCRP, but no use concentrations reported in the Council survey?

Non-Cosmetic Use - If use in laxative drugs is mentioned, use in other types of drugs as presented in FDA’s inactive ingredients database (http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm) should also be included. This database indicates that Sodium Sulfate is used in ophthalmic drug products at concentrations up to 1.2%, in inhalation products at up to 0.03% and in iv infusion products at up to 1.14%.

Toxicokinetics - In the summary from the original CIR report, please identify the radiolabel.

Genotoxicity, Summary - The description of the Ames test indicates that it was conducted at doses up to 5000 µg per plate. The Genotoxicity section and the Summary then state that no effects were observed at “5000 mg/L”. Which units are correct, µg per plate or mg/L?
Dermal Irritation and Sensitization, Summary - As the 3 month dermal study in which Sodium Sulfate was used a control also looked at hematology and histopathology of major organs, it should be presented in the Repeated-Dose exposure section, rather than dermal irritation. The lack of systemic effects observed in this study should also be mentioned in the Summary.

Table 1 - It is not clear where the 0.03% spray product came from. It is not known whether or not other fragrance preparations are spray products.
Memorandum

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

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

DATE: April 20, 2016

SUBJECT: Comments on Tentative Report Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics (posted April 12, 2016)

Introduction - It is not necessary to state that the original report was published in 2000 twice in the first two sentences of the Introduction.

Absorption, Distribution, Metabolism and Excretion - The information on acetaminophen metabolism does not seem relevant to this report. If it is left in the report, it should be placed after ADME information on Sodium Sulfate itself.

Short-Term Exposure, Summary - Generally, 90-days is not considered long enough to see "neoplastic" changes. The important point of this study, is that the only test-related histopathologic effects observed were in the skin. The statement in the Summary: "histopathology findings were non-neoplastic" should be revised to indicate that only effects on the skin were observed. Just stating that the "histopathology findings were non-neoplastic" implies that there were histopathology findings, when the only observations were effects on the skin.

Short-Term, Human, Discussion - It is not clear if the human occupational studies, described as "long-term" exposure should be in the "Short-Term Toxicity" section. Please indicate what was examined in the occupational exposure study, e.g., lung function, hematology, liver function tests.

Co-Carcinogenicity - Please revise the following sentence: "A test in which rats were fed Sodium Sulfate and had been injected with dimethylhydrazine (DMH) results showed few colon tumors in rats treated with Sodium Sulfate plus DMH compared to those treated with only DMH."

Irritation, Human - Please revise: "An experiment containing 1.8% Sodium Sulfate patch concentration..."