Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics

Status: Draft Tentative Amended Report for Panel Review
Release Date: August 22, 2019
Panel Date: September 16-17, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; 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 Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: August 22, 2019
Subject: Draft Tentative Amended Report on Capryloyl Salicylic Acid

Enclosed is a draft Tentative Amended Report on Capryloyl Salicylic Acid (*capryl092019rep*). An insufficient data announcement (IDA) on this ingredient was issued at the June 6-7, 2019 Panel meeting; the data requests were as follows:

- Impurities
- Phototoxicity

To date, there has been no response to the Panel's IDA on Capryloyl Salicylic Acid. It should be noted that report comments (*capryl092019pcpc*) that were received from the Council prior to the June Panel meeting have been addressed.

Also included in this package for your review are the flow chart (*capryl092019flow*), literature search strategy (*capryl092019strat*), ingredient data profile (*capryl092019prof*), CIR report history (*capryl092019hist*), 2019 FDA VCRP data (*capryl092019fda*), and minutes from the June Panel meeting (*capryl092019min*).

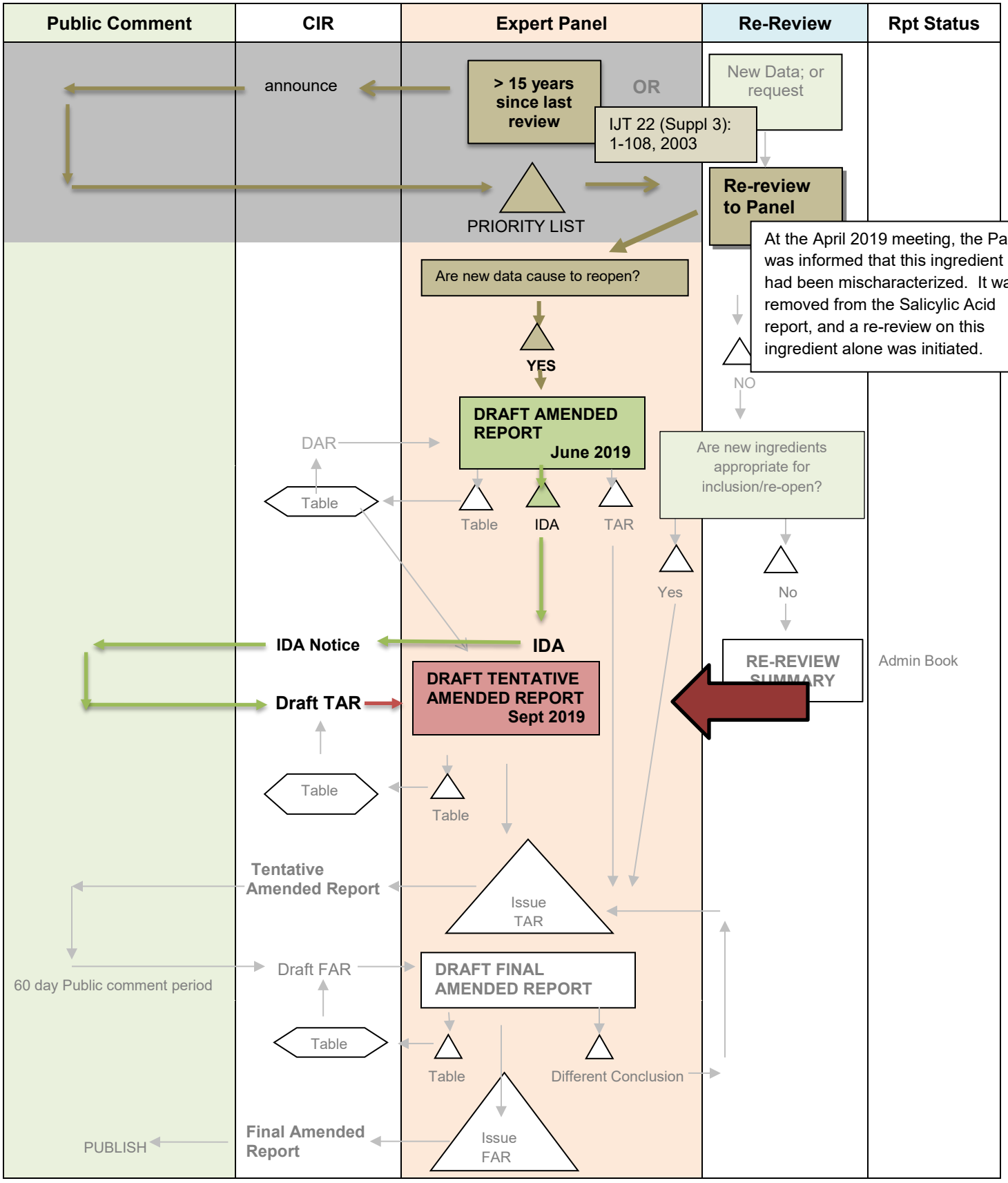
The Panel should carefully consider and discuss the data (or lack thereof) and the draft Discussion presented in this report, and issue a Tentative Amended Report with a safe, safe with qualifications, unsafe, or insufficient data conclusion.. If the data remain insufficient for making a determination of safety, then the Discussion should include a listing of the remaining data that are needed.

1620 L Street, NW Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Capryloyl Salicylic Acid

MEETING September 2019



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

CIR History of:

Capryloyl Salicylic Acid

Draft Amended Report, Teams/Panel: June 20-21, 2019

Capryloyl Salicylic was removed from the Salicylic Acid and Salicylates ingredient group (i.e., because it is a ketone, and not an ester) prior to the Panel's review of the Draft Final Amended Report at the April 2019 Panel meeting. A Final Amended Report on this group (minus Capryloyl Salicylic Acid) was issued at that meeting. A Draft Amended Report on Capryloyl Salicylic Acid that contains data on this ketone (identified by CAS No. 78418-01-6 and corresponding chemical names for this ketone) has been prepared for the Panel's review at this Panel meeting.

The Panel discussed the issue of skin sensitization potential for this ingredient. Capryloyl Salicylic Acid induced skin sensitization in guinea pig maximization tests at challenge concentrations of 0.5%, 2%, and 5%, but not at 1%. However, in HRIPTs, cosmetic products containing 0.5% or 2% Capryloyl Salicylic Acid were classified as non-sensitizing. After reviewing the HRIPT results and considering that the highest reported maximum use concentration of Capryloyl Salicylic Acid is 0.5% in leave-on cosmetic products, the Panel was reassured that the sensitization potential of exposure to this ingredient via cosmetic use is not a risk.

After reviewing the available data, the Panel issued an Insufficient Data Announcement (IDA) with the following data requests:

- Impurities
- Phototoxicity

Draft Tentative Amended Report, Teams/Panel: September 16-17, 2019

Report comments that were received from the Council prior to the June Panel meeting have been addressed. To date, there has been no response to the IDA that was issued at the June Panel meeting.

September 9-10, 1999 (72nd) Meeting of the CIR Expert Panel

Salicylic Acid, Calcium Salicylate, Magnesium Salicylate,
MEA-Salicylate, Potassium Salicylate, Sodium Salicylate,
TEA-Salicylate, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate,
Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate,
Myristyl Salicylate, Octyl Salicylate,Tridecyl Salicylate, Butyloctyl Salicylate,
and Hexyldodecyl Salicylate

Dr. Schroeter said that his Team determined that additional data are needed to complete the safety assessment on this group of ingredients. He noted that the data requests on this group of ingredients, also known as beta hydroxy acids, would be similar to those that were issued on the alpha hydroxy acids. Dr. Schroeter's Team issued the following informal data request:

(1) Data to determine dermal irritation that is pH-dependent, as well as concentration-dependent
(2) Data that determines the possibility of promotion of carcinogenicity, such as a dermal sunburn cell study of pyrimidine dimers and/or MEDs to determine the photosensitivity that may occur
(3) Request that industry submit information on any additional uses or expected uses of these ingredients

Dr. Schroeter indicated that a discussion of his Team's concern regarding the use of these ingredients on children and any toxicity needs to be developed, but this can be done at a later date, after data requested informally have been reviewed.

Dr. Belsito said that no additional studies on irritancy are needed because of data indicating that these ingredients can be used at a level that is nonirritating. He also said that the Panel could take the same approach that was used during its review of alpha hydroxy acids, to indicate that products containing these ingredients should be formulated so as to be nonirritating. Dr. Belsito indicated that the following data are needed:

(1) Risk assessment for teratogenicity
(2) Some type of study (similar to alpha hydroxy acid sunburn cell study or thymidine dimers study)
(3) Update on the ways in which these ingredients are being used in cosmetics

The combined list of data requests (both Teams) is as follows:
(1) A risk assessment for developmental/reproductive toxicity of concentrations delivered by cosmetic products alone and in combination with salicylic acid from other common sources (e.g., acne medications, aspirin, etc.)
(2) Additional uses intended by industry, i.e., exfoliant use
(3) Dermal irritation data using pH vs. concentration (like in the AHA report)
(4) Studies similar to those requested for the AHA report examining the effect of use and sun exposure, i.e., sunburn cell or pyrimidine dimer studies

Dr. Andersen said that the list of data requests will be provided to Dr. McEwen as an informal request for industry data.

Dr. Belsito noted that his Team had also discussed the possible exclusion of MEA and TEA Salicylate from the present report, given the ongoing research activities on the ethanolamines.

The Panel agreed that MEA and TEA Salicylate should remain in the present report.

February 14-15, 2000 (74th) Meeting of the CIR Expert Panel

Salicylic Acid, Calcium Salicylate, Magnesium Salicylate,
MEA-Salicylate, Potassium Salicylate, Sodium Salicylate,
TEA-Salicylate, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate,
Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate,
Myristyl Salicylate, Octyl Salicylate, Tridecyl Salicylate, Butyloctyl Salicylate,
and Hexyldodecyl Salicylate

Dr. Belsito noted that the following data on these ingredients were requested (informal data request) at the September 9-10, 1999 Panel meeting:

(1) A risk assessment for developmental/reproductive toxicity of concentrations delivered by cosmetic products alone and in combination with salicylic acid from other common sources (e.g., acne medications, aspirin, etc.)
(2) Additional uses intended by industry, i.e., exfoliant use
(3) Dermal irritation data using pH vs. concentration (like in the AHA report)
(4) Studies similar to those requested for the AHA report examining the effect of use and sun exposure, i.e., sunburn cell or pyrimidine dimer studies

Dr. Belsito also recalled that data on mutagenicity, phototoxicity, and skin irritation potential were received since the September Panel meeting. After considering these data along with the ingredient use concentration data, Dr. Belsito's Team concluded that Salicylic Acid and the other ingredients in this group are safe as used when formulated to avoid irritation and when formulated to avoid increased sun sensitivity. Furthermore, it was concluded that if these ingredients have an effect on sun sensitivity, it is expected that directions for use would include the daily use of sun protection.

Dr. Shank noted that the new data indicate that exposure to low ingredient concentrations in cosmetics leads to blood levels that would be considered insignificant.

Concerning the issue of exfoliant use, Dr. Bailey recalled that data on sunburn cell formation and MED's were included in the Panel's original request for data. He wanted to know whether the Panel plans to issue a safe as used conclusion in the absence of these data.

Dr. Belsito noted that Salicylic Acid and its salts are sunscreens to some extent. He also speculated that if the sunburn cell study were done, the results would indicate either no increase in sun sensitivity or protection against sun exposure; however, concern about the need for photoprotection would remain. Dr. Belsito also considered that the study results may be similar to those reported for AHA's, which would serve as the basis for restrictions/qualifications (proposed by Belsito Team) relating to the safe use of Salicylic Acid and its salts and esters.

Dr. Bailey expressed the view that the expectation is that industry will test products to determine whether or not there is any increase in sun sensitivity. This would entail the performance of both MED and sunburn cell studies.

The Panel voted unanimously in favor of issuing a Tentative Report with the conclusion that Salicylic Acid and its salts and esters are safe as used when formulated to avoid irritation, and when formulated to avoid increased sun sensitivity. It was also concluded that if enhanced sun sensitivity is expected, then directions for use including the daily use of sun protection should be provided.

September 11-12, 2000 (76th) Meeting of the CIR Expert Panel

Salicylic Acid, Calcium Salicylate, Magnesium Salicylate,
MEA-Salicylate, Potassium Salicylate, Sodium Salicylate,
TEA-Salicylate, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate,
Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate,
Myristyl Salicylate, Octyl Salicylate, Tridecyl Salicylate, Butyloctyl Salicylate,
and Hexyldodecyl Salicylate

Dr. Belsito stated that a tentative conclusion on the safety of these ingredients was issued at the February 14-15, 2000 Panel meeting. He then indicated that it has been requested that the Panel consider adding the ingredient, Amyl Salicylate to this review, with the understanding that this is the only salicylate listed in the International Cosmetic Ingredient Dictionary and Handbook that is not included. However, Dr. Belsito's Team noted that Amyl Salicylate is listed only as being used as a fragrance ingredient in cosmetics, and that assessing the safety of ingredients that function only as fragrance materials is not within the Panel's purview. Dr. Belsito recalled that Benzyl Salicylate (used as fragrance ingredient and UV light absorber) also is not included in the present review.

Dr. Schroeter asked for Dr. McEwen's opinion on the proposed addition of other salicylates to the present review.

Dr. McEwen said that one might expect that Amyl Salicylate might be used in a fashion that is similar to that of the other salicylates in the group. He added that because Benzyl Salicylate is an aromatic compound, it probably is not in the same family of use.

Dr. McEwen stated that his reason for requesting the addition of Amyl Salicylate to the present review is based on the observation that the data already in the report are applicable to this ingredient. He added that if an additional function(other than that of a fragrance material) is assigned to this ingredient in the future, it would then be a candidate for the CIR review process. Thus, issuing a conclusion on Amyl Salicylate now would be more feasible.

Dr. Andersen said that the CIR Procedures are very specific in terms of exempting fragrance ingredients from the review process, and that this is the reason why Amyl Salicylate is not included in the report that is being reviewed.

Dr. Bergfeld asked if it would be appropriate to include information on the chemistry of Amyl Salicylate in the current report even though its safety in cosmetics is not being evaluated, and to also indicate why this decision was made in the report discussion.

Dr. Andersen said that the rationale for excluding Amyl Salicylate from this review could be stated in the introduction and report discussion, and that the chemical structure could also be included in the report.

The Panel agreed that the current report should be revised to reflect the preceding comments on Amyl Salicylate by Drs. Bergfeld and Andersen.

The Panel voted unanimously in favor of issuing a Final Report on this group of ingredients with the following conclusion: Based on the available information, the CIR Expert Panel concluded that Salicylic Acid, the salts Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate, the esters Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate, and Tridecyl Salicylate, and the compounds Butyloctyl Salicylate and Hexyldodecyl Salicylate are safe as used when formulated to avoid irritation and when formulated to avoid increasing sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

June 4-5, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

Salicylic Acid and Salicylates

DR. BELSITO: Okay. You're ready, Wilbur. Thank you. This was a re-review that was given to us in Wave 2, and there was a final report on salicylic acid and 16 salicylates in 2003, so we need to re-review it. And if we need to open it, we need to open it, or we can open it to add on these four new salicylate groups; amyl salicylate, hexyl salicylate, isotridecyl, and silver salicylate. I just had a question for Dan. I was okay with all of them, but what about the silver?

DR. LIEBLER: I didn't throw it out right now, but, with an inorganic, it could be more about the silver than the salicylates. So, I would say actually, we could delete it as an add-on; it's not a no-brainer.

DR. BELSITO: Okay.

DR. LIEBLER: The others are fine.

DR. BELSITO: And then, having said that, in the original report we actually reviewed something, called capryloyl salicylic acid, that structurally looks very different from all the other salicylates. Should that be thrown out?

DR. LIEBLER: No, I thought that was okay. I mean, it's just esterifying the hydroxyl group next to the carboxylic acid on the salicylic. But it's similar enough to a salicylate that I think it belongs in the report.

DR. BELSITO: Okay.

DR. EISENMANN: My question is MEA salicylate, because it's in the MEA report and it has a more conservative conclusion in the MEA report. I don't know if you want to just leave it in the MEA report. In the MEA report it says, "safe in the present practice of use and concentration describe in the safety assessment, when formulated to be non-irritating, rinse-off products only. The Panel cautions the ingredients should not be used in product in which N-nitroso compounds may be formed." In that report, it's limited to rinse-off products only.

MR. JOHNSON: It also said when formulated to be non-irritating.

DR. EISENMANN: Right, when formulated to be non-irritating, right.

DR. BELSITO: Well, would that apply to TEA salicylate as well?

DR. EISENMANN: That was just in the Monoethanolamine report. No, I think TEA is salicylates; it's not involved.

DR. BELSITO: But weren't we told, somewhere in this document -- it's been awhile since I reviewed -- that these aren't metabolically broken down very easily on the skin? Because we're dealing with salicylic acid absorption? Wasn't there someplace in the report where it states that? Is it in the metabolism section?

DR. LIEBLER: Somewhere in the metabolism section, I think it referred to only a small percentage of the applied material was hydrolyze.

DR. BELSITO: Yeah, I seem to recall that.

DR. LIEBLER: Like 5 or 10 percent, maybe less than that even. And I don't think that's particularly noteworthy.

You know what? On second thought, I think we can get rid of the capryloyl salicylic acid. The more I think about that, the more I think that just doesn't go with the rest.

MS. KOWCZ: It's also used more as emollient.

DR. LIEBLER: It's a different use, okay.

MS. KOWCZ: Yes, it's a different use.

DR. BELSITO: So, we're removing it?

DR. LIEBLER: Yes.

MS. FIUME: So, procedurally, this is a re-review because it's been 15 years. And it was part of the original group.

DR. LIEBLER: It was part of the original group?

DR. BELSITO: So, we're including ingredients and we're --

MS. KOWCZ: Are we excluding any?

DR. LIEBLER: I don't remember ever taking one out of a re-review. All right. I won't fight the battle.

MS. FIUME: You can change is conclusion, or you can ask for information, if you don't think it's covered; but procedurally, I don't remember us removing one either.

DR. LIEBLER: We have enough new turf with polyaminopropyl biguanide, let's just leave it in.

DR. BELSITO: How do we review it? Do we have any data on it?

DR. BERGFELD: Do you have to review it now? You're just considering opening and adding four.

DR. BELSITO: I'm just pointing out that I don't know that there is data in the document to support it. Is there another group where it would more logically belong?

MS. FIUME: Salicylic acid is in this group, I guess that would be a question for Dr. Liebler. I mean, as I said, you can reopen if you don't think that the conclusion is still supported, or if the conclusion should have been different the first time around; and ask for information if you can't support the conclusion.

DR. BELSITO: Okay.

MS. FIUME: I just don't know if you can delete it, from the original group, because of re-review.

DR. LIEBLER: Yeah, I don't want to go there. We don't need to go there. Like I said, obviously the fact that at first I wanted it, and then I didn't want it, it's a close call. If it's already in there that's fine. Where I am on this, is reopen it and add the new ingredients, safe as used. But try and simplify the conclusion a little bit. See if we can take a run at that issue.

DR. BELSITO: I'm just curious, under cosmetic use; so, we see this huge increase in the amount of ethylhexyl salicylate and salicylic acid. Is that a huge increase because of cosmetic use, or is it a huge increase because of OTC use?

Because ethylhexyl salicylate is a sunscreen; and salicylic acid is an acne medication and a wart remover, that are both OTC. When you go out and do surveys, are you asking for cosmetic use?

DR. EISENMANN: Yes.

DR. BELSITO: Or are you asking for total sales?

DR. EISENMANN: No, I've been asking for cosmetic use.

DR. BELSITO: So, there's just a lot more cosmetic exfoliators and anti-aging creams putting salicylic acid and TEA salicylate into their formulas, is that it?

DR. EISENMANN: Don't know.

DR. BELSITO: Don't know. Okay. It's just, it's striking, the huge increase. It doesn't bother me in terms of safety.

MR. JOHNSON: Dr. Belsito, back to Carol's concern, should the MEA salicylate be deleted, you know, in that a published report on this ingredient occurred in 2015?

DR. BELSITO: Well the published report was on MEA, not MEA salicylates. The question was the MEA report was more restrictive.

DR. EISENMANN: But it included MEA salicylates in the report.

DR. BELSITO: It did?

DR. EISENMANN: Yes.

DR. BELSITO: Oh, I didn't realize that.

DR. EISENMANN: So, it's more restrictive based on the MEA, than on the salicylate.

MS. FIUME: And for that one I wouldn't necessarily have the same objection, because it has been looked at again; it's not that it's in 15 years it hasn't been reviewed.

DR. BELSITO: I don't know, Dan, what do you want to do?

DR. LIEBLER: If you won't get struck dead by lighting for deleting an ingredient from a re-review, then if we ended up reopening this, I think we could delete that because it's already been reviewed. Because it might have a different conclusion.

DR. BERGFELD: If you do that, then you can put that deletion to a discussion, and the reason why, and refer them to the other manuscript.

DR. LIEBLER: Yeah. Right.

DR. BELSITO: Okay. So, we're deleting MEA salicylate.

DR. BERGFELD: As you're thinking, I think we have to take another look at the conclusion.

DR. BELSITO: Well, before we get that.

DR. BERGFELD: When you get there.

DR. BELSITO: Yeah. I had a problem with a statement on Page 43 of the PDF. Under discussion, from published CIR Final Reports on Salicylates, it said, "The Panel did not consider it likely that consumers would simultaneously use multiple cosmetic products containing salicylic acid; thus, the serum levels of salicylic acid that will result for dermal application will likely be less than the serum levels from ingestion."

And now we have a huge number of uses for salicylic acid. We have a huge number of uses for ethylhexyl salicylate. I'll turn this over to my tox colleagues, but do you think that statement is still relevant? Or do we need a margin of exposure calculation, based off of absorption and aggregated exposure of multiple cosmetic products that might contain salicylates?

DR. SNYDER: What's the concentration in the sunscreen?

DR. BELSITO: Usually around five-ish percent.

DR. LIEBLER: There's a 5 percent max.

DR. BELSITO: But then you have salicylic acid in body washes for exfoliation. You have salicylates in other products.

DR. SNYDER: I was just thinking about 24-hour exposure in a sunscreen mode of application.

DR. LIEBLER: Yeah, but it's that low.

DR. BELSITO: But then it's not just sunscreen. So, you go out and you have a little dry skin, and you use a bath wash with salicylic acid to exfoliate a little bit, and then you put another chemical on that has --

MS. FIUME: That's a rinse-off.

DR. BELSITO: -- TEA salicylate. I'm just saying. You know, what we have here are -- you know, we've gone from two orders of magnitude, to three orders of magnitude, and cosmetics containing TEA -- or ethylhexyl salicylate. Presumably, we're told they're not sunscreen use, they're cosmetic use.

DR. BERGFELD: Lower percentage of concentration.

DR. BELSITO: What?

DR. BERGFELD: The concentration levels are reasonably low.

DR. BELSITO: But there are multiple products out there. I'm just pointing it out.

DR. LIEBLER: Yeah, the sentence actually compares the exposure to multiple products, from that which might be encountered by using a baby aspirin; which is, I believe, half of a 325mg dose.

DR. BELSITO: 81mg.

DR. LIEBLER: 81, okay. So, it's even less. Okay. For those that take aspirin, I don't know how many people -- maybe older people still take aspirin, but older people --

DR. KLAASSEN: Older than what?

DR. LIEBLER: You know.

DR. BELSITO: Yeah. Watch what you say, Dan.

DR. LIEBLER: Everybody in Kansas. I don't know, but it just seems to me like -- I don't know for sure, but I think the aspirin is kind of like the dial phone. Are people taking aspirin anymore, except for people are taking single tablet prescriptions for anti-platelet?

DR. BERGFELD: Pretty common.

DR. LIEBLER: Really?

DR. KLAASSEN: I think so.

DR. LIEBLER: Analgesic dosage?

DR. BERGFELD: Well they relate to baby aspirin, mainly.

DR. LIEBLER: Yeah, okay.

DR. BELSITO: No, but Dan's talking about using aspirin for analgesic.

DR. BERGFELD: I know.

DR. BELSITO: Like 325mg tablets, one or two.

DR. LIEBLER: As opposed to Ibuprofen and naproxen and so forth.

DR. BERGFELD: And NSAIDs.

DR. LIEBLER: Okay, maybe that's not the right issue to bring up then. So, I honestly don't know if that's true. I mean, I think you've got a good point, Don. If you were using more than one skincare product that contained a salicylate -- I mean these can be absorbed for sure. And if you do absorb them, what's the aggregate dosage from that versus your 81mg a day?

And that would require some consumer use data and -- that would require some data to do the calculation. I don't think we can just say that now and get away with it in a report.

DR. BELSITO: This also has to do with lack of reproductive and developmental toxicity seen. And quite honestly, most women of childbearing age are not taking 81mg of aspirin daily; it's being taken by people like Curt and I, who are not female and are well over 50. I mean, I just couldn't believe this language. This is a leap of faith to say that.

You know, we have data showing that there's reproductive toxicity, in terms of failing to close the ductus arteriosus as a result of aspirin; and then we're just saying, oh, well, there are no reports that 81mg causes a problem. And most pregnant women don't take aspirin, they take pre-natal vitamins and that's it.

DR. LIEBLER: So, you were on the panel that agreed to this language.

DR. BELSITO: I must had been sleeping.

DR. LIEBLER: Okay. But it might've been arguably true then; and it might arguably be not true now. Is what you're saying, basically.

DR. BELSITO: The levels of concern now are quite different from what they were 15 years ago; and the way we approach things are quite clearly different. So, I just don't agree with that statement.

You can make it. But then you better come up with some margins of safety or some data to compare what your tox endpoints are; which I presume with the DART effects, what the levels we're seeing in the DART effects, and what you would assume to be absorption of salicylates as in aggregate exposure in cosmetic products.

And I point that out, particularly, because of the huge increase in salicylic acid and ethylhexyl salicylate, which I hope you were going to tell me was all sunscreen in OTC, but it's not.

DR. LIEBLER: But if there's a lot of sunscreen in OTC and it's part of the body burden --

DR. BELSITO: Right. I mean, it's part of the --

DR. LIEBLER: -- then they added the amount from cosmetics, it's still worth considering.

DR. BELSITO: Exactly.

DR. LIEBLER: So, it's something we need to consider, whether or not it's true cosmetic uses. I don't think it's an issue we need to solve right now if we're going to -- we're basically talking about reopening the report, adding new ingredients, and then we'll deal with this later.

DR. BELSITO: Well, what I'm saying, is that when we reopen the report we cannot simply argue that we're blowing off the potential systemic toxicity of salicylic acid, based upon the fact that 81mg doesn't cause any issue. I mean that whole last sentence should go away.

DR. LIEBLER: Oh, I agree.

DR. BELSITO: And there should be a little bit better justification as to why we're not concerned about the DART effects from cosmetic exposure.

DR. LIEBLER: Right, I complete agree with that.

DR. BELSITO: David?

MR. STEINBERG: I think your comment on the use of ethylhexyl salicylate increase in cosmetics can be explained that OTC drugs, it's called octisalate.

MS. KOWCZ: Octyl silicide.

MR. STEINBERG: Octisalate.

MS. KOWCZ: Yeah.

MR. STEINBERG: Okay. And what happens is that, if you make cosmetic claims, your labeling for drug facts are totally different.

DR. BELSITO: Right.

MR. STEINBERG: So, a company who's making a sunscreen, using octisalate, might register as a cosmetic to show that they're actually making cosmetic claims, and they've registered it with the FDA. But instead of using the drug names they're using the INCI names.

So, it's possible that the surge has been the companies who want to cover themselves both ways. They're not selling it as a cosmetic, but they're registering it as a cosmetic. And now they might be selling it as a cosmetic for Europe or places where sunscreens are cosmetics.

And then again, they can't use our drug names, they have to use the INCI names. The surge could be explained that way.

DR. SNYDER: So, in those products, is it used as an active ingredient, or is it used as an inactive ingredient?

DR. BELSITO: Well except that the point that Wilma made, is when you do look at levels of use for ethylhexyl, they're not at levels that typically would be used in sunscreens.

MR. STEINBERG: What levels are they using?

DR. BELSITO: They're reporting use up to 5.1 percent in leave-ons. So, yeah, they are reporting them as sunscreen uses.

MR. STEINBERG: That's what I think it is. Now your question?

DR. SNYDER: In those products, is it used as an active ingredient, or is it used as some inactive component?

MR. STEINBERG: In the United States, it's an active ingredient. But you have to remember, that if you get outside of the United States, Australia, and Canada, sunscreens are all cosmetics. Okay, so you have totally different labeling issues.

DR. BELSITO: But the other thing, Paul, is when they might not market it as a sunscreen. If they market it as an anti-aging, then it will contain a sunscreen. So, it's just like there're a whole number of fragrance-free products out there that contain fragrances, because they're not added as fragrances supposedly.

DR. SNYDER: They're essential oils.

DR. BELSITO: Right, or biocides; some of the fragrances are biocides. I mean Cetaphil has farnesol in it. Farnesol is a fragrance, yet it's labeled fragrance-free.

DR. SNYDER: We have data under absorption. It says that a sunscreen was tested and only 1 to 2 percent is dermally absorbed. We're only talking 1 to 2 percent of maximum 5 percent. So again, I think we're --

DR. BELSITO: But that's one product.

DR. SNYDER: Right.

DR. BELSITO: So, we need to look at aggregate exposure; because these are used in a huge number of different products. We cannot simply say that the absorption -- we're looking at safety as used in cosmetics. And this is used in a huge number of cosmetic products. I don't understand the magnitude of increases that have occurred with the ethylhexyl salicylate and salicylic acid.

Are these being used in one product type, where it would be unlikely that I would use more than one body scrub or more than one anti-aging product? Or are they being used in a multitude of other products that I, as a consumer, might be using, like a shampoo, a conditioner, a hair gel, a body moisturizer, a facial sunscreen, yada, yada, yada.

I don't know. You know, it's just usage has increased dramatically. And I think that we need to know what kind of products these increases have occurred in, so we get some sense of what the aggregate exposure of the consumer is.

Because right now we have no good data. We have absorption of a sunscreen, we had some data, again, I believe, that says that on the skin these esters don't metabolize to much sal acid. Is that correct? It's just doing this off of memory. Where's the ADME here?

So, methyl salicylate. If you look at methyl salicylate it says, "The presence of unhydrolyzed methyl salicylate was only observed at the 30-minute timepoint. The fraction of methyl salicylate observed in tissues as a proportion of total salicylate varied from 0 to .26." Then it says, "The tissue and plasma concentrations after application of methyl salicylate increased rapidly within the first hour of application." It was rats. But it doesn't tell you the total absorption, it just says the concentrations increased rapidly in the first hour.

And then they looked at site-specific absorption. And they found the usual variation of behind the ear 11 micrograms/cm2 per minute, initial flux, the abdomen, 3. And 1 to 2 percent of the sunscreen in the applied product was absorbed. But it doesn't tell you which sunscreen, because it was an aggregate of sunscreens. Hexyl salicylate, micrograms/m2, it's pretty low, 4.1 micrograms/1.4m2. What's the average body surface area, two point something m2?

DR. KLAASSEN: I don't know off the top of my head.

MS. FIUME: Don, as you're looking at that, as far as usage for ethylhexyl salicylate, on PDF Page 166, there are probably over 2,000 uses that are used in fragrances. 1,200 are cologne and toilet waters, almost 650 of perfumes, and 422 are other fragrance preparations.

So, for the ethylhexyl salicylate, that's probably where a large number of those come in. As far as looking to see how these are being used, a salicylic acid, it is used probably in almost every category; half are rinse-off, half are leave-on. But it's used in probably almost every category reported to FDA.

DR. BELSITO: So, the mean male body surface area peaks at about 2 m2. And the mean female peaks at about 1.8 m2.

DR. SNYDER: So, your only concern is that the difference between the 2003 report, and this report, is that we have this markedly increase number of uses?

DR. BELSITO: Well, my concern, too, is that our argument for why we weren't concern about DART effects in the prior report is bogus.

DR. SNYDER: Well, maybe not. I mean we had -- there's five pages of dermal absorption studies in that old report. Table 8 --

DR. BELSITO: I understand. But we were basically saying, you know, in the discussion, that we weren't worried because people take baby aspirin and we're not seeing that. That's not the way we should approach it, that's all I'm saying.

DR. SNYDER: Okay. So, our current conclusion discussion could talk about an accumulative effect with multiple product use. And to make that scientifically sound, we need some kind of a number to do some kind of an aggregate max worst case scenario exposure is what you need.

DR. BELSITO: Right.

DR. SNYDER: Okay. But I don't know that we can get that.

DR. BELSITO: You can get it. The fragrance industry gets it all the time. You should be able to get it. There are habits and practices that tell you what -- I mean, right, Dan? Creme Global has that.

DR. LIEBLER: Right.

DR. BELSITO: And you can look at the product types and you can look at the ranges of the various salicylates. You could assume a worst-case scenario of absorption from the salicylates, and you can come up with a number.

DR. SNYDER: Did we have a NOAEL for the reported effects.

DR. BELSITO: DART effects?

DR. SNYDER: I'm looking back at the old report and I'm having a hard time finding it.

DR. BELSITO: No, I don't think we do. There are just clinical reports of patent ductus arteriosus, with -- you know, salicylism and the effects of salicylism.

I don't think there are dose responses; which is why I think we came up with this bogus claim that saying, well 81mg is not likely cosmetic exposure; it's going to result in the same exposure as low-dose aspirin and we don't see problems with that. I just think that argument is -- I mean, it just doesn't cut science in 2018.

DR. BERGFELD: It sounds, to me, like we're taking on a new tact, and that tact is to get the aggregate information, because we've mentioned it now in two or three documents. And so maybe it should be, when Carol makes the call, that we ask for that immediately up front.

DR. SNYDER: This is a re-review, so we can say, during this meeting, we agreed to reopen and here are now the issues that we are concerned about.

DR. BELSITO: Right. That's what I'm saying. Yeah, I'm not making a big deal of it. I'm just saying that we can't use the argument, we used before, to dismiss the DART effects.

DR. SNYDER: So, like we would come up with a --

DR. BELSITO: So, as you're looking at trying to accumulate data, please try and find us any information you can get on dose response relationships for the DART effects of salicylic acid and salicylism, in terms of, you know, hearing and all the other side effects of excess salicylic acid. All we have are really just more case reports, someone consumed a whole jar of aspirin and presented to an emergency room, and here were the symptoms.

Okay, so we're going to reopen the report. We're going to add everything but silver. We're going to delete MEA. And we're going to leave capryloyl salicylic in there for now; but caution we may not be able to rule on its safety.

MS. FIUME: Well, it sounds like you're going to be issuing an IDA, based on what the conversation has just demonstrated.

DR. BELSITO: Yes.

MS. FIUME: If there are data that can help you rule on the safety of that ingredient, that can be part of your IDA; if there's specific information, that you're missing, that you feel you need to rule on the safety of that ingredient, since you're reopening anyway.

DR. BELSITO: Well, Dan, what I'm hearing from you is that the rest of these salicylates are not really good read-acrosses, would that be fair?

DR. LIEBLER: For?

DR. BELSITO: Capryloyl salicylic acid.

DR. LIEBLER: They're all going to differ substantially in dermal penetrations, just based on the size of the molecules. The methyl salicylate, being the smallest, might be best penetrator. And it said esterifies would probably penetrate better than the salicylic acid. And the others will probably decline with the size of the substituents.

DR. BELSITO: Basically, I'm just searching the document for what we have on capryloyl salicylic acid. We have a case report of an allergy, and a woman with dermatitis of the face. And they thought it was not due to the capryloyl salicylic acid, but a structural isomer, the 3-capryloyl salicylic acid -- whatever that means -- that was a contaminant. And basically, that is it.

And then we have a split clinical report, split-face, 44 female volunteers. No significant changes in erythema, so I guess not irritating. And then case reports of that positive patch test; and that's it. So, we have very little data on it.

If you think the toxicity is going to be different, we don't have method of manufacture. We don't have impurities. We have no tox data. We have no data, essentially, except for case reports. So, are we going to needs -- based upon your looking at this molecule, are we going to need data for it?

DR. LIEBLER: For the?

DR. BELSITO: Capryloyl.

DR. LIEBLER: Capryloyl, no. I mean as far as its absorption, distribution, and its pharmacology toxicology, I think it's going to be pretty similar. So, you know, I don't think this stuff is going to get absorbed very much.

DR. BELSITO: Okay. So, you think that we can use the rest of the materials here as read-across to go with the safety of this, even though, structurally, it's a different molecule.

DR. LIEBLER: Yeah, it's not dramatically different. And so, I think it's reasonable to read across from any several of the others here of what we've got.

DR. BELSITO: Okay. So, we're not asking for any additional data on this, because we have none.

DR. LIEBLER: I don't think we need it.

DR. BELSITO: Okay.

MS. FIUME: Don? PDF Page 131, does --

DR. SNYDER: It's a risk assessment.

MS. FIUME: Does that help you? Does that help inform any of the decisions for salicylic acid; and how much is actually absorbed, based on the new data that you have, now, with increase use?

DR. BELSITO: Actually, there's a lot of dermal data on methyl salicylate. There's oral exposure data on salicylic.

DR. SNYDER: And that section that Monice is talking about, they actually tested a facial product containing 2 percent. And they referenced that to 20 percent of that following the ingestion of a single baby aspirin.

DR. BELSITO: Yeah, I think this data is great. So, I guess I didn't go and look at it because I didn't think we had the data given the way we put it in the discussion. But we clearly have the data to -- I mean, this just needs a lot more summarization, under the DART, than what's currently done in the document.

MS. FIUME: We'll take care of that.

DR. BELSITO: Yeah, I think we'll be fine. And then we just need to change the way we discuss it. We need to summarize this huge amount of data, and whatever we can, so we're not accused of double dipping our data in the publication.

DR. SNYDER: To your point, this is actually referenced in the other document as a risk assessment support, so we could add that.

DR. BELSITO: Yes.

DR. SNYDER: That based upon a previous risk assessment, we still don't need --

DR. BELSITO: Yeah. And then bring into the document. Yeah. I mean, we need to, in the summary, instead of just saying associated with developmental toxicity, give the NOECs, more than just saying associated. So, a little bit more information when we're summarizing what we previously saw.

MS. FIUME: We'll go ahead and expand that.

DR. BELSITO: And then I think develop in the discussion, a little bit better point that given the levels of use in cosmetics, the absorptions that we've seen, the relative lack of metabolism of the esters to salicylic acid in the skin, that these levels would not likely be achieved with cosmetic use.

DR. BERGFELD: In summary, you're going to reorganize this material, and you're going to go with it?

DR. BELSITO: Yeah, we're going to drop silver. We're going to keep capryloyl salicylate. We're just going to beef of the summary of the DART sections from the prior reports. We're going to drop that silly comment that taking 81mg of aspirin isn't a problem, so we're not worried about reproductive toxicity; and we're going to strengthen that argument with a little science. And add in the other salicylate other than silver.

DR. BERGFELD: There's no insufficient data announcement or request?

DR. BELSITO: Not at this point. Dan, are you comfortable going with safe as used?

DR. BERGFELD: Are you retracting the need for aggregate information regarding --

DR. BELSITO: Yeah. I think that when you look at the dose levels that were used in the DART studies, you know, again, if you start summarizing them rather than simply saying there were teratogenic effects; yeah, we have NOAELs. We have huge NOAELs that we can go by; and we can incorporate them into our discussion to show the margin of safety in cosmetics is sufficient.

MR. JOHNSON: Dr. Belsito, are there any concerns about estrogenic activity, comedogenicity or skin sensitization potential?

DR. BELSITO: Well, the comedogenicity really surprise me because we use those for acne treatment. So, I didn't understand that at all. But in terms of sensitization, I think that --

DR. SNYDER: Sun sensitivity is addressed in the old report.

DR. BELSITO: Oh, you mean in terms of sun protection? Yeah. I think that that type of language probably should be maintained. The conclusion, in terms of with use of sunscreen -- how was it worded? It was somewhere between the alpha hydroxy acid report and this. We weren't as harsh with the restriction. But yeah, that restriction should remain, just because of stripping of the stratum corneum.

DR. BERGFELD: Is that in the discussion or the conclusion?

DR. BELSITO: No, it was actually in the conclusion of the old one. Like the alpha-hydroxy.

DR. SNYDER: Page 42, second and third paragraph.

DR. BELSITO: Our conclusion was, based on the available data, expert panel conclude, yada, yada, yada, yada, are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

DR. BERGFELD: You want to keep all that?

DR. BELSITO: Yep. Do you?

DR. BERGFELD: Well, how did we handle the alpha-hydroxy as this is a beta-hydroxyl.

DR. BELSITO: That was even stronger in the conclusion. That was not if, that was needs to be labeled.

DR. BERGFELD: I think it was a SPF of 2 had to cover that.

DR. BELSITO: No, we didn't put an SPF.

DR. BERGFELD: No, but I think that was, you had to have a SPF 2 to protect with the alpha-hydroxy.

DR. SNYDER: Dialkyl Dimer.

DR. BELSITO: What?

DR. SNYDER: Dialkyl Dimers?

DR. BELSITO: You trying to move on?

DR. KLAASSEN: How'd you get that idea?

MS. FIUME: It actually refer to MED.

DR. BERGFELD: Are you looking at the outside document?

MS. FIUME: SPF 4.

DR. BERGFELD: A 4. It was high as 4? Was it in the discussion, or was it in the conclusion?

MS. FIUME: It was added as a note, added and approved to the conclusion.

DR. BERGFELD: Okay.

DR. BELSITO: Okay.

MS. FIUME: I didn't look at the re-review.

DR. BELSITO: So again, we need to summarize the DART data a little bit better in this re-review. And the conclusion will be pretty much what we had before, with a sun sensitivity.

MR. JOHNSON: Are there any concerns about the sensitization potential --

DR. BELSITO: No.

MR. JOHNSON: -- for hexyl salicylate?

DR. BELSITO: What?

MR. JOHNSON: Hexyl salicylate. Because like we have positive guinea pig sensitization data on Page 30. And also human sensitization data on Page 34.

DR. BELSITO: So, we have a LLNA of .18 percent. And it was noted that this was very low, maybe due to its irritating properties, or sensitizing impurities. And then DRAS (phonetic) testing showed some alert sensitization reactions.

And then in a photo allergy test in guinea pigs, it was negative. And they were topically challenged with 50 percent. I did not make much of those other tests, so I'm not concern. And then they did a Magnusson Kligman guinea pig maximization test; and a challenge at 10 percent hexyl salicylate, no sensitization reactions were observed. So, no I'm not concerned. Okay? No, I'm not concerned.

MR. JOHNSON: Okay. What about the human data on Page 34?

DR. BELSITO: I'm not concerned. I'm not concerned. I'm concerned about irritation, not sensitization. Okay? Done? Paul, you're happy?

DR. SNYDER: Yeah.

DR. BELSITO: Okay.

June 4-5, 2018 CIR Expert Panel Meeting – Dr. Marks'Team

Salicylic acid and Salicylates

DR. MARKS: Yes. The salicylates. This is a re-review document on the salicylates. In 2003, a final report was published on salicylic acid and 16 salicylates. The conclusion of these ingredients are safe as used when formulated to avoid skin irritation, and when formulated avoid increasing the sun sensitivity. Or when increased sun sensitivity would be expected. Directions for use include the daily use of sun protection.

You didn't like that previous conclusion, this one is really -- and then let me see here.

DR. SLAGA: Sound like Trump put that together.

DR. MARKS: What else do I have here. Exfoliate -- reopen question mark. Then there was a question of adding four new ingredients. Were they okay. And actually, I had to dig for those, Wilbur. Did you put those four ingredients on this memo right at the beginning? If you look at page 4. Let's see, where are they? Nope, that's not the right one. Let me see, what was the other page I had.

MR. JOHNSON: They're in the Introduction.

DR. MARKS: Yeah, 13. Is that right, page 13?

MR. JOHNSON: Page 12.

DR. MARKS: Twelve, okay. Actually 13. Yeah and the four ingredients that would be added are the ones -- so I'm on page 13. Those four at the end of the list with the asterisk. The amyl, hexyl, isotridecyl and the silver -- oh, here's silver again, Ron Hill. Silver salicylate. So, they would be the four add-ons.

I guess the first question is, do we want to reopen this and massage the conclusion; or do we want to just leave it the way it is? And then the second question is, do we want to reopen it to add these ingredients and is that a no-brainer? And once we open it, are we going to have a no-brainer or are we going to spend a lot of time on a conclusion?

DR. SHANK: I have a question. The new data came in, it's on page 26. Two references on salicylic acid, dermal application to pregnant women; it suggests that it could cause ductus arteriosus and oligohydramnios. I think we should read -- at least I should read -- I couldn't get them.

DR. MARKS: And this is new.

DR. SHANK: Yes, it's new. Because that could potentially change the conclusion. But I haven't read the paper, so I don't know.

DR. MARKS: So, page 26, under relevant studies, the estrogenic activity?

DR. SHANK: Let me look.

DR. HILL: No, it's above that. Right at the top of the page.

DR. MARKS: Oh, okay. Under salicylic acid. It's that first paragraph?

DR. HILL: Um hmm.

DR. MARKS: The NTP?

DR. HILL: Um hmm. Is that not the one?

DR. MARKS: Creams containing salicylic were applied to skin groups of 18 and 18 -- that's mice.

DR. HILL: That's not the ductus -- no, that's not the one.

DR. MARKS: You mentioned this is other relevant -- this is to pregnant females this was applied, and there was question. Were they pregnant female animals or humans?

DR. SHANK: Women. Humans.

DR. MARKS: Yeah.

MR. JOHNSON: That's on page 24.

DR. SHANK: Twenty-four?

DR. MARKS: Twenty-four.

DR. SHANK: Thank you.

MR. JOHNSON: You're welcome. Under dermal and salicylic acid -- human dermal salicylic acid.

DR. MARKS: There's dermal, oral.

DR. HELDRETH: That's 25. Page 25.

DR. MARKS: Human dermal -- yeah, we're on 25. Oh, can potentially cause early closure of the ductus arteriosus and oligohydramnios. Therefore, it should not be applied over large surface areas for prolonged time periods or under occlusive dressing. That may enhance systemic absorption.

I like this, the primary reference upon which these statements are based has been ordered for

further details. Okay. So, with that alone, new data, we have to reopen it.

DR. SHANK: Yeah, it caught my eye.

DR. MARKS: I would agree.

MR. JOHNSON: Now, I note that reproductive and development toxicity are addressed in the discussion section of the final report on salicylic acid.

DR. SHANK: The old report?

MR. JOHNSON: Yes. That discussion is in this report.

DR. SHANK: Okay.

DR. MARKS: What page were you on?

DR. SHANK: Where can I find it?

DR. MARKS: So premature closure, the ductus arteriosus probably -- maybe that's not a bad thing. But you wonder if there's so much absorption, and this is occurring prematurely --

DR. SHANK: If it happens in utero, the baby dies.

DR. MARKS: Yes.

MR. JOHNSON: It's on page -- I think, for some reason, I'm one page off. It begins on page 43, I think, because mine says 42.

DR. SHANK: Forty-three?

MR. JOHNSON: Yes.

DR. HELDRETH: It's actually 42.

MR. JOHNSON: It is 42? So that's right this time. Page 42.

DR. SHANK: Forty-two?

MR. JOHNSON: Right.

DR. HELDRETH: You'll see some italicized text there.

DR. SHANK: I'm going there.

DR. MARKS: You're going there. Page 24.

MR. JOHNSON: Yeah. It's the last paragraph.

DR. MARKS: So that's reproductive tox --

DR. SHANK: Was it a positive patch test on 42?

DR. HELDRETH: So, at the bottom of 42 bleeding onto to 43, the paragraph that starts with reproductive and developmental tox associated with.

DR. SHANK: Okay. Thank you. Well, I think we need to read the new papers.

DR. SLAGA: Yeah. I sent them to several people.

MR. JOHNSON: And also, in the other team, it was mentioned that the reproductive and developmental toxicity data in the published file report should be included, you know, in summary form and this safety attachment. Because the summary, as written, contains very few or no details regarding dosage and no effect levels.

DR. SHANK: Okay.

DR. MARKS: So, we handle this by reopening with an insufficient data notice -- or announcement? Because we can move on to a tentative.

DR. SHANK: Well, I'd like to read the papers.

DR. MARKS: Oh. Well, then would you table it?

DR. SLAGA: Until we get those papers?

DR. SHANK: Can you get those papers?

DR. HELDRETH: We're going to get the papers and we can incorporate them in the draft iteration.

MR. JOHNSON: You mean the two that relate to ductus arteriosus?

DR. SHANK: Yes.

MR. JOHNSON: Just those publications?

DR. SHANK: Those two.

MR. JOHNSON: Just those. Okay. Yeah, we'll probably have those.

DR. SHANK: For some reason I couldn't get them.

MR. JOHNSON: Okay.

DR. SHANK: Just an abstract, but I couldn't read the paper.

MR. JOHNSON: I might add the MEA-salicylate safety assessment on that ingredient was published in 2015. So, this is an ingredient that really should be considered for re-review. So, should that MEA-salicylate be removed from this document?

MS. LORETZ: It has a different conclusion; so that, I think, would be reason to perhaps remove it. It has some complexity there.

DR. HILL: Say what you said again.

MS. LORETZ: It has a different conclusion.

DR. HILL: What Wilbur said.

MS. LORETZ: Oh, I'm sorry.

DR. HILL: No, that's all right. I heard you.

MR. JOHNSON: Yeah, I was saying that a final report was published in 2015, in which a MEA-salicylate was one of the ingredients in that review. So that means, given the 15 year, you know, timetable for re-review, that would not fit into that scheme.

So, with that in mind, should MEA-salicylate be removed from this document?

DR. HILL: What do we have in the way of hard data? I mean, it still fits -- so that must have been the MEA group, right? Yeah. But from a salicylate standpoint, it definitely fits here too.

DR. MARKS: So, does that get two asterisks, previously reviewed? Because that's important particularly if the conclusion of the MEA-salicylates don't have all these restrictive language in it. Sun sensitivity, direction for use of sun protection.

MS. LORETZ: Except that it's restricted to rinse off products. So, it goes both ways.

MR. JOHNSON: And there's also, you know, when formulated to nonirritating as a qualification as well.

DR. MARKS: Well, that's in the present -- the rest of these ingredients that were reviewed all have the irritation -- to avoid irritation. But if rinsed off -- that's interesting.

DR. ANSELL: Is the argument that the MEA-salicylate data would help inform the discussion of this salicylate group? I mean, we could bring the data in without --

DR. HELDRETH: It's in the original, so --

DR. ANSELL: -- could then draw a conclusion about --

DR. HELDRETH: It was in the original so it's a matter of kind of taking it out.

MR. JOHNSON: And there would be a brief summary in the safety assessment, you know, regarding any data that were in the original published file report on salicylates and salicylic acid.

DR. MARKS: If there's a previous report, it's just a couple years old and it was limited to rinse offs and avoid irritation. Why would it be included in this one, other than it has salicylate in the title?

DR. SHANK: Depends on if you want to keep them in the family.

DR. MARKS: Well, you could start doing that with a lot of things. I assume that the MEA-salicylate, there was a whole different family with that. Was that based on the MEA?

DR. HELDRETH: Yeah, called MEA --

DR. MARKS: Not the salicylates, yeah. So now we could be double dipping in a lot of things if we do that. I don't see, as you said I think, Jay, unless it adds something to the toxicologic data in this report, why add as an ingredient? The other, if it does, we've done this before. Just mention it in the report, the pertinent toxicologic --

DR. SHANK: Developmental tox was not a problem for the MEA salicylate was it?

DR. MARKS: I can't imagine it was.

DR. HILL: It not listed in the VCRP as being in use or in the concentration survey.

DR. MARKS: Okay.

DR. HILL: In the data table that we got with this report.

DR. MARKS: Okay. So that means that it probably was just included as part of the group. And the group as a whole we said rinse off.

DR. HILL: And there was actually discussion as to whether to keep it in with Dr. Anderson, Belsito and -- yeah, so this was in 1999. Way before my -- Dr. Schroder was still on the panel then.

DR. MARKS: So, team, what do we want to do? Now another thing has come up with the MEA salicylates. Let's kind of dispense with that. Do we want to keep it in this report or not? Remove it and it's already been reviewed. You said that was just 2015, Wilbur, right?

MR. JOHNSON: That's right. Published in 2015.

DR. HELDRETH: Right. So it came out in IJT in 2015. That means that we likely looked at it in 2012.

DR. HILL: Was it in use then or did we just read across without really further consideration of the salicylate aspect, which I hate to think might have happened, but.

DR. MARKS: My feeling is remove it.

DR. SHANK: So, I'm confused.
DR. HELDRETH: No. It wasn't reported to be in use at the time.
DR. HILL: There's nothing else popping up here at all.
DR. HELDRETH: So, likely it would not be informative.
DR. SLAGA: You know what year the two papers related to --
MR. JOHNSON: Ductus arteriosus?
DR. SLAGA: -- the pregnant women --
MR. JOHNSON: Ductus arteriosus?
DR. SLAGA: Yeah.
MR. JOHNSON: Let me check.
DR. SLAGA: It's been very, very recent?
DR. SHANK: So, what is the question on MEA salicylate? It's not in the old report and not a suggested add-on.
DR. HILL: I thought it was a suggested add-on.
DR. SHANK: It is?
DR. MARKS: It's a suggested add-on.
DR. HILL: Yes.
DR. MARKS: Yes.
DR. HELDRETH: MEA?
DR. MARKS: It's right here. It's in the first column there. See it?
DR. ANSELL: Even though it has its own -- it's already been reviewed within the last --
DR. HILL: And that was his question.
DR. SHANK: Okay. It's just not in the table. All right.
DR. HILL: No. It's not in the read across table.
DR. MARKS: Oh, it isn't?
MR. JOHNSON: Dr. Slaga, those were published in 2008 and 2016.
DR. SLAGA: If that amyl was -- let's say it was possibly, you know, that was reviewed in between so to speak.
MR. JOHNSON: Oh. Yeah.
DR. HILL: It's not a proposed add-on. It was already there in the original report, in the salicylate report.
DR. ANSELL: It was?
DR. HILL: That's what it says here in the original salicylates report. And somehow it ended up in the MEA report.
MR. JOHNSON: Right.
DR. MARKS: Okay. So, it's not an add-on.
DR. SHANK: It's not in the data profile.
DR. HILL: It's not an add-on.
DR. HELDRETH: Let's not forget the other add-ons, though, that this team suggested, the titanium.
DR. HILL: I did.
DR. MARKS: No, it isn't. I was going to bring that up, but thank you, Bart. So actually, I mean, we have to include the MEA salicylate in this, if it's in the original report.
DR. HELDRETH: You don't have to. It's up to you. It already has a new conclusion. But if you feel, for some reason, it would be helpful to this report, you can choose to include it.
DR. MARKS: That comes down to, obviously, if we don't reopen it, it stays there. We made a decision to reopen?
DR. SLAGA: No. Well other than --
DR. SHANK: Well, I guess table because --
DR. MARKS: We have the pregnancy issue.
DR. HELDRETH: It's either reopen or table it.
DR. SHANK: That's the issue. And if those paper shows there's a real problem --
DR. SLAGA: They may not.
DR. SHANK: In the original review, they were worried about reproductive developmental toxicity. And said the concentrations in cosmetics are so low, it's not going to be a problem. But now with the new data, I think we should read that.

DR. HELDRETH: So, at his point we can reopen it to look at the new data. And in the next iteration of the report that data will be put in there. If you look at that data and decide you know what, this was no big deal, nothing's changed, then you can close it out and put out a re-review summary.

DR. SHANK: Okay.

DR. HELDRETH: Like we would if we never opened in the first place. But if you decide to open it for add-ons, you can still continue it. But, it's the panel's prerogative.

DR. ANSELL: Yeah, I guess this is exactly what the reopens intended. There's new data that people want, but not prejudge what it'll do to the conclusion.

DR. SLAGA: Very good.

DR. HILL: I have a question for Wilbur. In your read across table on page 5 -- because I didn't go back and look at everything in the old reporting detail yet. If there's an X in the box, is that old data plus new data?

MR. JOHNSON: Yes.

DR. HILL: Okay. Because there's no data, whatsoever, on capryloyl salicylic acid, which is an interesting compound. It's disparate from the others. And it looks like lipophilic aspirin.

MR. JOHNSON: Yes.

DR. HILL: And aspirin is a unique compound, because irreversibly acetylate serine and cyclooxygenase is one in two. So, it's an irreversible cyclooxygenase inhibitor.

And I don't know if this one does or not, but it appears that that was handled strictly by read across in the original report. Because the only thing we shown here is case report.

But there is reported use now for up to 62 percent, if it's accurate, in a leave-on formulation; which got my attention because most of these salicylates are reporting use below 1 percent. And then there are a small number that are at 5 percent, 3 percent. Most of them are below 1 percent. And so, I wondered how we managed to read across to that in the absence of data.

DR. HELDRETH: Just to be clear, it wasn't my fault.

DR. HILL: No, I didn't say it was. I wasn't here either.

DR. HELDRETH: I didn't include that search outlier. I wasn't here.

DR. HILL: But I'm just saying it seem like -- and there's quite a few uses if I'm not mistaken. Most of them, I think, the concentration might be low. But that 62 percent certainly got my attention, if that's accurate.

DR. MARKS: Well, that actually feeds into my question. No sensitization data, however. on page 50 that capryloyl salicylic acid leave-on is 63 percent.

DR. HILL: Right.

DR. MARKS: Rounding off, it's 62.9. And salicylic acid is 30 percent. And that 30 percent for salicylic acid, if these concentrations are correct, then we need the irritation sensitization. Particularly if you look at the look at the local lymph node assay, that was positive with salicylic acid at 20 percent. I'd want to see HRIPT at 30 percent.

So, that would be when we reopen; and I'd like to see irritation and sensitization data on the capryloyl salicylate acid, and the salicylic acid at their highest use concentration.

DR. ANSELL: They're probably neutralized. They're not going to be --

DR. SHANK: We can do that in formulation, right?

DR. MARKS: Yes.

DR. SHANK: Not pure salicylic, yeah.

DR. ANSELL: It would be pH adjusted, so you'd really be testing the salt.

DR. MARKS: So, you're saying because it's a salt, we don't have to worry about it?

DR. ANSELL: No. But I don't want -- you know, you won't get a HRIPT on salicylic acid.

DR. MARKS: Right.

DR. ANSELL: You're going to get a HRIPT on --

DR. MARKS: Some ingredient.

DR. HILL: Salicylate solution.

DR. ANSELL: A salicylate solution, which has been pH adjusted or probably a formulation which contains it at some level. But even there -- I mean some of them are going to be --

DR. MARKS: I guess I'd want to make sure it's both neither -- at that concentration, it's neither an irritant or sensitization. If it's being used at that concentration, it should be.

DR. ANSELL: Some of the products are intended to be irritating, right? Aren't they face scrubs and --

DR. STEINBERG: Twenty percent is a wart remover.

DR. ANSELL: Yeah. So, we'd have titrate, exactly, where in between cosmetic and wart remover, we wanted to test them. Because we're pretty sure the wart remover is going to be irritating.

DR. MARKS: No question of that.

DR. SLAGA: They're going to be something.

DR. MARKS: It's actually interesting now you bring that up; because they're 40 percent salicylic acid plasters which clearly cause irritation. This is of course OTC drug. And that data could be brought into this just to support it.

And I'm not aware -- I can't remember seeing sensitization to a 40 percent salicylic acid plaster. It would be nice to just have that in there. Either that or we can say the expert opinion at 30 percent -- it's clearly irritating; I agree with you, Jay, no question about that. But sensitization, I don't think is an issue either.

DR. SLAGA: It shouldn't be.

DR. MARKS: So, do we want to request that or just say the expert opinion in the discussion, we know that OTC drug at 40 -- not just 20. But MediPlast is the brand name. That's at 40 percent. And it's used for both calluses and warts. Mainly for calluses. And as I said, I've never seen allergic contact dermatitis to that.

DR. STEINBERG: I think it's an NDA drug, not a monograph drug. There's a monograph for wart removers and it's 20 percent. I think it's 19 or 20 percent.

DR. MARKS: It's 17 percent in a liquid and actually to get the increased efficacy. I suggest to my patients use the plaster. And then now you're going up to 40 percent.

DR. ANSELL: Yeah. The ones you --

DR. MARKS: So, I guess the question is, can we get any data on that? Or just say the expert opinion is we know it causes irritation. And we have in there these products should be formulated so they're nonirritating. So that covers that. Even at 30 percent it covers it.

DR. ANSELL: The question would be what data would you want? Because we know it's going to be irritating so that's not -- we've answered that question.

DR. MARKS: Yeah. Now how about the capryloyl salicylic acid at 63 percent? I'm not aware of a medical use of that. Do we know that that's -- I would assume that's very irritating. But again, when you put formulate to be nonirritating, you've covered that issue. And I assume it's a non-sensitizer.

DR. ANSELL: I guess it depends where you tie it.

DR. STEINBERG: You're tying up the hydroxy group and leaving it free.

DR. ANSELL: I mean, if it's an ester then --

DR. HILL: No. But the carboxylic acid part of salicylic acid is free in that compound.

DR. ANSELL: Yeah. Then it would be --

DR. STEINBERG: Yeah. But the phenolic group is not.

DR. HILL: But the phenolic group is esterified uniquely in that one, compared to all the rest.

DR. MARKS: Interesting. As I mentioned, there was a local lymph node assay; that's page 119. Which suggests that 20 percent salicylic acid is a sensitizer. But in point of fact, and clinical experience, I haven't seen it with 40 percent. Did I interpret that right, Jay? Page 119.

DR. ANSELL: Yeah. Sensitization --

DR. MARKS: And those concentrations are correct, right, Wilbur? Because they are, I think, higher than the original report.

MR. JOHNSON: What page are you on?

DR. MARKS: Page 50, I think, is where they had the concentrations.

MR. JOHNSON: Fifty, okay. On the capryloyl?

DR. MARKS: Yeah.

MR. JOHNSON: Yeah. That's correct value.

DR. MARKS: Yeah. That's 62.9 and --

DR. HILL: What's odd about that is that everything else reported for that particular compound is very low.

DR. MARKS: Yeah. That's why I wanted -- and if you look at salicylic acid the range is huge; .000001 to 30 percent. Did I read the local lymph node assay right, Jay? That 20 percent is a sensitizer?

DR. ANSELL: I'm not seeing it on 114.

DR. MARKS: No, 119.

DR. ANSELL: Oh, 119. Salicylic acid, yeah the LLNA was --

DR. MARKS: Yeah. If you look under the sensitization salicylic acid on the right-hand column. Toward the bottom of that second paragraph from the bottom, 20 percent salicylic acid produced a .9, 1.8 and 7.2-

fold increase, a positive response.

DR. ANSELL: So, they're saying the highest concentration, 20 percent in acetone --

DR. MARKS: Gave a 7.2-fold increase, which would be a sensitizer. But I think if we had from MediPlast that there's no incidence of sensitization with that, that's fine with me. And I would have thought I would have seen that multiple times over the years. Okay.

MR. JOHNSON: But Dr. Marks, that 62.9 percent of concentration relates to use in body and hand products, not spray products.

DR. MARKS: Right. Leave-on.

DR. HILL: Leave-on, that's the point.

DR. MARKS: Yeah.

DR. ANSELL: And then the next one is kind of an odd 20 percent acetone/olive oil, and those were sacked by IP injection?

DR. MARKS: Yeah. I didn't --

DR. ANSELL: And they didn't find any significant T-cell proliferation.

DR. SLAGA: Could it be something with the acetone working?

DR. ANSELL: Yeah. Well, or --

DR. SLAGA: Helps things penetrate a lot better.

DR. ANSELL: And the use of salicylic acid does -- just as an acid at 20 percent.

DR. MARKS: Okay. So maybe I'll forego those issues with irritation sensitization, because we have the irritation in the conclusion as it stands now. Right now, if we reopen, what we really want to see is what's the reproductive and developmental toxicity of salicylic acid and that's relevant to those papers which -- on page 24 that you highlighted, Ron Shank.

Do we have any other needs? And we still haven't voted or commented on the add-ons.

MR. JOHNSON: Dr. Marks, before I forget, you know, are there any concerns about estrogenic activity?

DR. HILL: Estrogenic?

MR. JOHNSON: Yes. On page 26.

DR. MARKS: You're in the endocrine -- 26.

MR. JOHNSON: The data indicate that butyloctyl salicylate binds to the estrogen receptor.

DR. HILL: Yeah, but not very strongly. I mean, it appears to be a very weak binder.

MR. JOHNSON: Okay.

DR. MARKS: Does that need to be put in the discussion or that's obvious when you look in here?

DR. SHANK: I don't think so.

DR. MARKS: Not in the discussion, Ron Shank?

DR. SHANK: I don't think so.

DR. MARKS: Yeah, okay. Okay so let's go to the add-ons because we didn't really settle on that. So, we have now five add-ons. It would be amyl, hexyl, isotridecyl, silver and titanium. You brought the titanium from the other report. Do you like those add-ons?

DR. SLAGA: Seems okay to me.

DR. MARKS: If we include the add-ons, then it's going to move forward. We will reopen and have a new report.

DR. SLAGA: Yeah.

DR. MARKS: And then in the interim we'll get that clarified as far as the reproductive and developmental.

DR. SHANK: Is the silver a no brainer?

DR. HILL: Probably not.

DR. ANSELL: So, if we choose to reopen for data purposes, then we would discuss the add-ons?

DR. SLAGA: Right.

DR. MARKS: Yes.

DR. ANSELL: Okay.

DR. HELDRETH: We can do it either way.

DR. ANSELL: Yes, but one way I argue. The other way I just nod my head.

DR. HELDRETH: We can choose to reopen and add or just reopen based on data.

DR. MARKS: Well, we're reopening at this point based on --

DR. SHANK: New data.

DR. MARKS: -- the new data for the reproductive and developmental toxicity. Clarify that.

DR. HELDRETH: So, the current salicylates in there that are salts are all just alkyl and earth metals, instead of being a transition metal like silver or titanium.

DR. HILL: Yeah. There is that although --

DR. HELDRETH: But is that significant?

DR. HILL: Titanium is actually not really a true transition element. It's a group for --

DR. HELDRETH: Right. But definitely different than the --

DR. HILL: I guess it might be regarded as such. Huh?

DR. HELDRETH: Definitely different than the alkaline earth metals.

DR. HILL: Oh yeah, it definitely is. I mean, we didn't have any data on it, as I recall, in the survey. And it would be nice to know more of the chemistry. So maybe I'm just -- doesn't need to be.

DR. MARKS: Do you want yes for those five?

MR. JOHNSON: What about the silver salicylate? Is that going to remain or be removed?

DR. MARKS: Well, that's why I said for those five. That includes silver and titanium.

MR. JOHNSON: Okay.

DR. MARKS: Sounds like not discussion in terms of amyl, hexyl or isotridecyl. Those are no-brainers it sounds like. Silver?

DR. ANSELL: I only see two asterisks.

DR. HILL: Page 14.

DR. MARKS: I'm on page 13. Is this not correct?

MR. JOHNSON: There are four.

DR. MARKS: Yeah. There are four. Right here. And there are the four.

DR. ANSELL: Okay.

DR. MARKS: And then what we decided to do was add the titanium also from the salicylate report which we -- I mean, from the titanium. The organo-titanium or however we're going to -- maybe we'll just call it titanium ingredients. Okay, team?

DR. SLAGA: Add them.

DR. MARKS: Add them. Ron Shank, add all five?

DR. SHANK: Okay.

DR. MARKS: Yup.

DR. HILL: Okay.

DR. MARKS: Okay. Good. So tomorrow I'll move we open the salicylate report from 2003, and what we want to clarify is the new data on reproductive and development toxicity of salicylic acid, which was on page 24. We want to review those original papers. And then we want to add on the amyl, hexyl, isotridecyl, sliver and titanium salicylates.

Now, I almost hate to bring this up, but we're going to have to cross this path anyway. Do we like the conclusion with all this sun business? It seems cumbersome to me, but I don't know which way to -- you know, now since we've reopened it, we're going to put add-ons, we have the opportunity to change the conclusion.

Safe for use when formulated to avoid skin -- and when formulated to avoid increasing the skin's sun sensitivity. And I'm sure that's because the exfoliant nature of salicylic acid. If it's formulated to be nonirritating, is it really exfoliant?

MS. LORETZ: Also, there's an NTP report that shows that it's protective against sun damage. And that was subsequent to the last report. So that could affect that recommendation.

DR. MARKS: Oh. Nonirritating, and NTP report that it was protective, you said, Linda?

MS. LORETZ: Yeah.

DR. SLAGA: It's protecting against the sun, yeah.

DR. MARKS: And what page is that on?

DR. HELDRETH: PDF page 26.

DR. ANSELL: It hasn't been added.

DR. MARKS: Oh, it hasn't been added yet.

DR. HELDRETH: No. It's in there. PDF page 26.

DR. MARKS: Okay.

DR. HELDRETH: Very top of the page.

DR. MARKS: That's what I want, page 26.

DR. HILL: Protection is tumor formation.

DR. MARKS: Sun -- it reduce tumor -- photo-tumor induction?

DR. HILL: Mm-hmm. Some protective affect against photo-carcinogenicity at lower intensities.

DR. MARKS: Okay. And obviously, that would be highlighted in the discussion because it's a significant change in the -- any other?

So, do you like that -- although we aren't to the conclusion, at this point, because we aren't going to suggest reopening a tentative report; but presumably we're going to move to a tentative report with formulated to be nonirritating, and get rid of all the sun business, at least at this point.

Does that sound reasonable, Tom? And we can obviously go back. But I kind of, as you know, like thinking ahead. And I like that we have -- it seems to me it's the irritating part, which would be really concerning with sun exposure. Because you would induce more potential for sunburn. And if the NTP report says it's sun protective --

DR. SLAGA: Well, that's probably the lower concentration protects against skin-induced tumors.

DR. ANSELL: Well, it seems to parallel the alpha hydroxy acid language.

DR. SLAGA: Yeah.

DR. ANSELL: I don't know whether that's relevant here or not.

DR. HILL: Yeah. They're talking about skin abrasion, or what's the word I'm looking for?

DR. MARKS: Yeah, exfoliant.

DR. HILL: Exfoliation. Yes.

DR. MARKS: Basically. removing the stratum corneum.

DR. HILL: So, increasing sun sensitivity.

DR. MARKS: Yes.

DR. HILL: But it has a sunscreen affect. Probably similar to PABA in terms of its sun screening.

DR. MARKS: It's not phototoxic. Okay. So, I'm going to move, tomorrow, we reopen it. And get more data from the original papers on the reproductive and development toxicity of salicylic acid. We add on the amyl, hexyl, isotridecyl, sliver, titanium salicylates. And we're going to suggest that a conclusion will be formulate when nonirritating down the line. But we're just reopening at this point.

DR. HILL: I would like to know more about the basis for the read across to the capryloyl compound, which is mostly used at low concentrations. But again, would seem to be a lipophilic aspirin.

Is there any biological data on that compound out there at all, at the moment? We seem to have this prohibition of looking at anything that resembles pharmacology, which I find very artificial.

DR. MARKS: Okay.

DR. HILL: And also, one more question was the butyloctyl salicylate is used at up to 35 percent in a lipstick. But I only found sensitization data to 5 percent in the old report.

DR. MARKS: That one I missed. The butyl --

DR. HILL: Butyloctyl. If you go to page 172, is it, somewhere near the end. I'm looking. Page 172, 35.9 percent. Also, 10 percent in a body and hand products, not spray. And 5 to 10 percent in other skin preparations. Suntan products, up to 10 percent, not spray.

But I only saw sensitization -- well, what I saw when I just looked at the old report is that they did the initiating at 5 percent. But then they came back and patch tested at 50 and 100. So they did -- was it the induction phase, you call it, at 5 percent, initially. I found it in the report and I left it.

DR. MARKS: Well, let's see what falls out with the reopening. Any other comments?

DR. SHANK: Not from me.

DR. MARKS: Okay. Anything else? Did I skip any ingredients? Any other unfinished business? If not, I think we'll adjourn.

June 4-5, 2018 CIR Expert Panel Meeting – Full Panel

Salicylic Acid and Salicylates

DR. MARKS: Okay. The salicylates. This is a re-review document on the salicylates. A final report was issued by the expert panel on salicylic acid and 16 salicylates, which was published in 2003.

The conclusion was that the safety assessment, that these ingredients are safe as used when formulated to avoid skin irritation, and when formulated to avoid increasing sun sensitivity, or when increased sun sensitivity would be expected; directions for use include the daily use of sun protection. So, it's a pretty long conclusion.

And then there was a suggestion to add five new ingredients, amyl, hexyl, isotridecyl and silver salicylates.

Our team felt we should reopen this. So that's a motion, I guess?

DR. BERGFELD: Yes.

DR. MARKS: And including in that motion would be to issue a tentative amended report, with a conclusion safe when formulated to be nonirritating, with these ingredients.

DR. BERGFELD: You're changing the conclusion as well?

DR. MARKS: Exactly.

DR. BERGFELD: Okay.

DR. MARKS: We made it simpler. In the discussion concerning sun sensitivities, since that was prominently mentioned in the previous conclusion, we felt that because it would be formulated to be nonirritating, because there's an NTP report, which found sun protective effect on carcinogenicity by the salicylates, and then it was non-phototoxic, that we could change the conclusion. But we would handle that in the discussion.

DR. BERGFELD: And that's a motion?

DR. MARKS: Yes.

DR. BERGFELD: Motion to reopened with those comments.

DR. HILL: Did you talk about the add-ons in that motion?

DR. MARKS: Yes.

DR. HILL: Okay, I missed that.

DR. MARKS: Yeah, those five new ingredients would be included in the reopened report, with a tentative amended.

DR. HILL: So, five would include the titanium that we just talked about --

DR. MARKS: No. I'm sorry, four. Four new ingredients; yeah, I didn't eliminate that one. I had the ingredients right, the number wrong, it's four. As was proposed in this, we decided not to move the titanium salicylate over to this report.

DR. BERGFELD: Is there a second or comment?

DR. BELSITO: Yeah, we did not feel that silver salicylate belonged in this group; that the toxicity would be driven by the silver and not the salicylate. I'll let Dan comment.

DR. LIEBLER: That's exactly how I felt. It's not a no-brainer; add-ons are no-brainers, this one's not, in my opinion. So, otherwise, I'm fine with the add-ons.

DR. BERGFELD: Do you want to reconsider your motion then?

DR. MARKS: Yeah, that's fine. We actually had that discussion back and forth and decided to include it; but, Dan, well taken, and we'll eliminate silver.

DR. BERGFELD: So, motion is just for four ingredients.

DR. MARKS: It will be three add-ons.

DR. BERGFELD: Three add-ons. Okay. Goes from five to three.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion regarding this re-review?

DR. BELSITO: No, I think Jim pointed out, very correctly, about the issue of the sun sensitivity and why we're slightly changing our conclusion to be a little bit more simpler and when formulating to be nonirritating. But that should be part of the discussion why we've changed that.

DR. BERGFELD: Okay. Ron Hill?

DR. HILL: I don't know why we are sufficient where the capryloyl -- that's a mouthful. That molecule is quite disparate than the others. It's actually a lipophilic aspirin. Aspirin has the ability, uniquely, among all nonsteroidal and disparate from all other salicylates, to acetylate cyclooxygenase irreversibly.

We don't have information on this particular molecule, at least not available in the old report, and

I didn't see anything new yet to indicate whether that can or cannot happen. And we have no biological data on that molecule, at all, based on what Wilbur told us yesterday and what's in the read across table. And I don't know if that was an oversight in the original report. I looked to see what, if anything, in the original report addressed that and there really was nothing, because there isn't anything.

So, for me, I would like to have an insufficiency for essentially everything related to biology for that capryloyl. But I wasn't around for the previous review, so.

DR. BERGFELD: Dan, do you want to comment on that?

DR. LIEBLER: I noted the chemical difference -- this is a little bit of an oddball -- but it was in the previous report. And the fact is, is that although the esterification, the attachment of the lipophilic modifier, is on a different site, when metabolized, you get back salicylate and capryloyl acid.

So, I didn't really feel that this was enough of an unknown quantity to be of concern. And I think that even if the data were a little thin on this one, the other materials would allow us to read across satisfactorily.

DR. HILL: My point is, and I've looked at the mechanistic detail of nonsteroidal anti-inflammatories repeatedly, and over the years, and follow this story, and I teach in this area at multiple levels. Aspirin does something different than everything else. If we can be sure that this particular molecule does not enter the binding pocket of cyclooxygenases, all is well.

But we have a lipophilic aspirin that should be very dermally penetrable, based on its log P, despite the presence of the carboxylic acid and based on its physical chemical properties. And I can't read across to it. Based on the possibility that it could irreversibly acetylate comparably to aspirin, cyclooxygenases; and there's lots of skin biochemistry involving cyclooxygenases in the skin itself, even if it doesn't make the systemic circulation. I put that out there as a comment, for me, it's insufficient.

DR. BERGFELD: Curt, do you want to respond?

DR. KLAASSEN: But isn't the acetylation of the COX due to the acetyl part of the acetylsalicylic acid?

DR. HILL: Yes, which is exactly what you've got with the acetyl moiety of the capryloyl, and this is the only one that's like that versus all the rest. So, if you look at the exact molecular mechanism by which -- and a lot is known about this now -- by which that acetyl group gets transfer to the serine of cyclooxygenase, which is the business end of cyclooxygenase. This could do that provided it can get into the binding pocket very nicely and comparably. There would be nothing to shut down that mechanism, if it could get in there and bind.

And I would be stunned if there isn't some information somewhere about that molecule. So, if it's being used as a skin anti-inflammatory, that potentially makes it a drug and not a cosmetic.

DR. LIEBLER: So, one of my best friends is one of the world leading authorities on cyclooxygenase biochemistry, and I've endured hole after hole of cyclooxygenase trivia. I can't exactly answer Ron's question, but I know there's enough data out there to be able to say whether or not this molecule would be able to access the active site of cyclooxygenases. I'd say let's keep it in and we can deal with that later.

DR. HILL: I didn't suggest removing it. I just said for me it's insufficient.

DR. MARKS: Okay. And then the other discussant point I'd like to bring up -- I think, Dan, that's an excellent suggestion. And then we'll figure out whether we want to make it insufficient the next time around.

Ron Shank pointed out, on Page 25 of the document, under Human Dermal Salicylic Acid, the paragraph there, in the third trimester, the use of Salicylic Acid can potentially cause early closure of ductus arteriosus and oligohydramnios. Therefore, it should not be applied over large surface areas for prolonged time periods, or under occlusive dressings that may enhance systemic toxicity. And Ron wanted to see the primary references on that, but I wonder what your team felt about that statement. Because I think, obviously, that raises a red flag and either we have to deal with it in a discussion or -- I don't think we can leave it hanging without addressing that.

DR. BELSITO: This was part of the discussion that we had, that we really need to do a margin of safety calculation based off of the absorption; particularly, in light of the significant increase in number of cosmetic products. And, again, I specifically asked Carol whether the huge increase in salicylic acid and ethylhexyl salicylate were due to over-the-counter products, i.e., exfoliants for acne for salicylic acid, and sunscreens for ethylhexyl salicylate. And I was told no they are cosmetic uses that have increased.

Our explanation, quite honestly, in the original report was quite lame. It basically said the exposure assessment contends that the reproductive and developmental toxicity, from a daily use of baby aspirin, is not significant. I don't know that we know that, how many pregnant women take baby aspirin.

I think we do need to go back in the document and do some margin of exposure, to assure that the absorption from aggregate use of these products would be below levels that would cause any type of reproductive

toxicity. But it is clearly known that aspirin does do that.

DR. HILL: And this is again, in my mind, when I was concerned about the capryloyl, because the log P of capryloyl analog is 3.9; that's right in the spot for transdermal delivery. If you're going to transdermal deliver a drug, the molecular weight needs to be low like that, and log P of four to six is the sweet spot, and we're right at four.

So, again, we don't have concentrations of use, that's the other issue here; if we knew that it was low, fine. But that's a serious, serious, potential biological effect were it to turn out that this would have high cyclooxygenase-inhibiting activity, plus the possibility of systemic availability.

DR. BERGFELD: Well the motions been made and seconded to reopen. And so, all of these discussant points will be recorded in the minutes and hopefully those that we'll address later. Obviously, at that time when we're readdressing it, it's possible to relieve or move out some of these ingredients, and to also address some of these issues. So, if we can call for the vote now, all those in favor of reopening?

DR. HELDRETH: Excuse me, hold on. Coming out of our re-review here, we either need to put out an insufficient data announcement, or we put out a draft tentative report.

DR. MARKS: The motion was to reopen, issue a tentative amended report, safe when formulated to be nonirritating and address these issues the next time around.

DR. BERGFELD: And that was seconded, I believe.

DR. BELSITO: Right. But we also discussed deleting the MEA salicylate because of restrictions on MEA. And actually, that MEA salicylate was in the MEA report. Deleting that would just leave it with MEA and not in this report.

DR. BERGFELD: Can we do that automatically now?

DR. HELDRETH: Yes. That already has a new conclusion and that's the one that will stand for that one, and it'll just continue with that report.

DR. MARKS: Right. And we're just adding three new ingredients.

DR. BERGFELD: Okay. Wilbur?

MR. JOHNSON: Back to Dr. Hill's concern about the capryloyl salicylic acid, what is happening with that?

DR. BERGFELD: My understanding is it's being left in for now. Is that correct? Ron Hill? Capryloyl?

DR. HILL: Yes. But if we're not going out insufficient on that, then I'm going to vote against the tentative amended report.

DR. BERGFELD: Dr. Marks, you want to respond to that?

DR. MARKS: Let's take the vote.

DR. BERGFELD: Okay. All those in favor of reopening and a tentative amended report, please indicate by raising your hand. Against? One opposed. Okay. And that will be recorded in our minutes. So, we don't have to deal with the salicylates anymore, we have dealt with them.

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DR. BELSITO: So, in 2003, we reviewed Salicylic Acid and 16 salicylates, so it was time for re-review. We decided to add on a few more salicylates and look at the whole package. That's what we have here. I said safe as used when formulated to be non-irritating and non-sensitizing. The question I had is Amyl Salicylate is listed only as a fragrance ingredient. Yet, it's in this report. Shouldn't it be dropped? Its function, if you look, it's just fragrance, as opposed to hexyl cinnamate, which has nonfragrance functions -- or Hexyl Salicylate rather.

DR. HELDRETH: According to our procedures, any specific ingredient to review, of which may otherwise be deferred, shall none the less be included at the discretion of the expert panel when other chemically related or otherwise conveniently grouped ingredients are considered. So, if the panel feels it helps to have that ingredient in there, whether it be for data or otherwise, it is their prerogative to use it.

DR. BELSITO: But should it be among the ingredients listed as we are reviewing? We can certainly rely on the data, but right now it's listed as one of the materials we're reviewing. No?

DR. HELDRETH: Yes. The way that the procedures are written, if it's incorporated in there, it's counted, if you're assessing the safety of it. Now, the panel has the prerogative to choose not to have it in the report at all, but that's your choice.

DR. BELSITO: I don't care one way or the other. I just was under the assumption that if it were fragrance only, we weren't reviewing it.

DR. HELDRETH: It's a reason that it may be excluded.

DR. BELSITO: Okay. Then, I guess, I had a question. If you look at the use limits for Salicylic Acid and TEA-Salicylate, we're exceeding the limits that the EU talks about. I didn't understand this on PDF 41, where it says that it was a maximum of 0.5 percent acid as preservatives. But not as preservatives, there's no restriction? I didn't understand that. "The European Union has established a maximum use concentration of 0.5 percent acid for the following ingredients as preservatives."

DR. EISENMANN: It's in the preservative, right?

DR. BELSITO: I understand. But is the limit only if they say they're using it as a preservative? And if they're not using it as a preservative, they can go above 0.5? Which is how I'd interpreted it. Then it begs the question, why they set that limit? Because we have Salicylic Acid being used at a much higher concentration than .5 percent. We're covering it by saying not sensitizing, right -- or irritating, rather? I just found it very curious that, in parenthesis, (as preservatives); it didn't make any sense to me. Because TEA-Salicylate and Salicylic Acid are both above those 0.5 percent levels.

DR. EISENMANN: It's also on Annex 3. I don't know the details of what it says on Annex 3. So it's in the preservative annex and it's on Annex 3. I don't know the details of the Annex. I'd have to find the report and look at it.

DR. BELSITO: It didn't bother me. I was just curious as to how and why they set that limit. And then I made a note to myself and failed to do it. They restricted baby products. Is it listed to be used in any baby products? No reported --

DR. BERGFELD: No, none reported, no.

DR. EISENMANN: One thing is, there's an opinion that's not finalized yet versus the regulation, so it has to be clarified a little bit. Remember the opinion that's not finalized has some of this additional warning. He's, like, intertwined what's the regulation and what's the opinion, and so that kind of has to be separated. Because the opinion has not been finalized, and has not been made into a regulation yet.

DR. BELSITO: Okay.

MR. JOHNSON: About the baby product, Sodium Salicylate is being used in baby shampoos at maximum use concentrations up to 0.31 percent. That's the only ingredient used in baby products.

DR. HELDRETH: For concentration of use. Salicylic Acid has two reported uses, according to VCRP, in baby products.

MR. JOHNSON: I'm just referring to the concentration data.

DR. BELSITO: I have a question, Wilbur, on page 59 where we're looking at LLNA was used to evaluate the effects of inhalation exposure. It says, "Methyl Salicylate (a respiratory and skin irritant) served as the negative control in both assays." Normally, you don't use skin irritants as a control for the LLNA.

MR. JOHNSON: That is as stated in the report, Dr. Belsito.

DR. BELSITO: Then another question on PDF page 61, the in vitro sensitization, you see, " The allergen–peptide/protein interaction in vitro assay." Is that the direct peptide reactivity assay?

MR. JOHNSON: That's one of the three assays that was used.

DR. BELSITO: But is it the DPRA, because I've never heard of that assay.

MR. JOHNSON: Actually, I mentioned three in vitro methods: One is the direct peptide reactivity assay. The other one is the SENS-IS assay. That assay measures the gene expression of irritation and the sensitization biomarkers. And the h-CLAT. I'm sorry the other one was --

DR. BELSITO: That was the old one? Right. So, you have the h-CLAT. So the allergen-peptide/protein interaction is the DPRA?

MR. JOHNSON: DPRA measures reactivity with mock peptides.

DR. BELSITO: I know what DPRA measures, Wilber. What I'm asking you is, in the first paragraph you say, "allergen peptide/protein interaction in vitro assay." Is that the DPRA? Because I'd never --

MR. JOHNSON: Yes.

DR. BELSITO: -- then it should just be DPRA.

MR. JOHNSON: Okay.

DR. LIEBLER: Wait a second. Are you talking about on Page 61, under sensitization in vitro, the first sentence?

DR. KLAASSEN: Third sentence.

DR. LIEBLER: Okay. Third sentence, "the allergen–peptide/protein interaction in vitro." Okay.

DR. BELSITO: Okay. Then in the discussion, PDF page 72, the first paragraph you say, "When formulated to avoid increasing the skin's sun sensitivity." I thought we were getting rid of that restriction based upon the data we have here. Because we actually saw that Salicylic Acid reduced the incidents of photo --

DR. EISENMANN: He's discussing what the conclusion was on the old report, I think.

DR. BELSITO: But this should not be in the discussion of the current report.

MR. JOHNSON: Okay. That will be deleted.

DR. LIEBLER: So, do you want to just delete that entire first paragraph, the discussion?

MR. JOHNSON: Yes.

DR. BELSITO: Yeah.

DR. LIEBLER: Okay.

DR. KLAASSEN: And I think this was also stated earlier in the report. You have the same sentence, and I think that needs to be clarified. Now it is true that in 2003, we thought this, but not anymore because we now have data. We'll have to make sure that it's clear.

MR. JOHNSON: Sure.

DR. BELSITO: So, say safe as used when formulated to be non-irritating and non-sensitizing. Are we all good with that?

DR. LIEBLER: I agree.

DR. SNYDER: Agree.

DR. BELSITO: Yes, Wilber.

MR. JOHNSON: A handout was distributed this morning. It contains IFRA's limits on Hexyl Salicylate. And one of the limitations relates to use in products that are applied to the lip. And Butyloctyl Salicylate is used in concentrations above 30 percent in lipstick. And this 1 percent limit is for products that are applied to the lip. So, are there any concerns about that high concentration in relation to IFRA's limit?

DR. BELSITO: Yeah, because we're now saying that you have to formulate it to -- IFRA's limit was based upon a QRA for Hexyl Salicylate. I don't know what the QRA would come out for this specific salicylate, but what we're saying is not, safe as currently used; we're saying safe as used when formulated to be non-irritating and non-sensitizing. They could apply a QRA for that product or whatever. That concentration reported here may be unsafe. We don't know.

This is not a blanket, okay, safe as reported in this, this is -- we're restricting it. I don't care what the concentrations are here. What I'm saying is some of them may be wrong. Companies need to do their homework.

DR. LIEBLER: Right. I think that's the only way we can deal with this, because we don't know, Butyloctyl Salicylate is a bigger molecule or hydrophobic, less likely penetration in the epidermis than Hexyl Salicylate. So, the numbers, if they did a QRA for Butyloctyl, would probably be substantially different. I think, we can't know that, so we just say, when formulated to be non-irritating, non-sensitizing.

MR. JOHNSON: Yeah, because the tentative conclusion that was issued stated, safe when formulated to be non-irritating.

DR. BELSITO: There's been no tentative. This is the first time we're looking at this whole group.

MR. JOHNSON: What, salicylates?

DR. BELSITO: The 2003 said non-irritating, but this is the first time -- I mean, we didn't come

out with a conclusion in 2018 or 17. We added four ingredients, and this is a complete, new relook. And we're changing -- we're saying non-irritating, non-sensitizing.

DR. LIEBLER: Wilber, the conclusion you have at the top of PDF page 74, says formulating to be non-irritating. Is that simply distilled down from the previous report, and you take out the sun UV exposure stuff?

DR. BELSITO: The previous report from 2003, correct.

DR. LIEBLER: Correct. Is that what you're referring to, Wilber?

MR. JOHNSON: No, the panel, at the June meeting, issued a tentative amended report with the safe when formulated to be non-irritating conclusion. So, that was the tentative amended conclusion.

DR. BELSITO: No, we determined to reopen the safety assessment to amend the conclusion. That MEA-Salicylate would not be included. Yeah, I guess.

DR. LIEBLER: Wilber's right.

DR. BELSITO: We're reassessing it, so we're changing the conclusion.

DR. LIEBLER: Right.

DR. HELDRETH: It's more restrictive. So, it likely should go out again.

DR. KLAASSEN: I have a question on page 67, right before the summary. We have a margin of safety, and I don't quite understand how that was calculated. It says, from 125 to 2.5 million, which is a pretty big range. But how did we -- I guess we calculated that or --

DR. SNYDER: Yeah. Mm-hmm.

DR. KLAASSEN: How?

DR. BELSITO: Eighty-seven.

DR. KLAASSEN: No, it's page 67.

DR. BELSITO: Sixty-seven.

DR. KLAASSEN: I mean, it says, with the assumption of 12 to 100 percent bioavailability, which is an 8-fold difference.

DR. BELSITO: That's RIFM's safety assessment.

MR. JOHNSON: No, the risk assessment is on PDF page 56, that we did, our calculations.

DR. HELDRETH: He's talking about what's on page 67, the RIFM safety assessment.

MR. JOHNSON: That's RIFMs, yeah, that's not ours.

DR. KLAASSEN: It says, "Depending upon the assumption of either 12-30 or 100 percent." But the difference between 12 and 100 is 8-fold. Then there's 125; if you multiply that by 8, it would be a thousand, but it's two and a half million. That's what I'm confused about.

MR. JOHNSON: Well, that is taken directly from the RIFM safety assessment on salicylates, Dr. Klaassen.

DR. LIEBLER: So, you can see how it seems inconsistent. It seems like it doesn't make sense. And I noticed the same thing with the numbers not scaling in parallel. If indeed that's taken correctly from the RIFM assessment, and there's not a number problem there, then there's something else about the calculation, having to do with more than probably the assumption of bioavailability.

DR. BELSITO: Well, it's product use. Remember RIFM has access to the Creme database.

DR. LIEBLER: Right.

DR. BELSITO: So, they know 95 percentile across all cosmetic products.

DR. LIEBLER: So, you need to change that sentence to bioavailability and product use.

MR. JOHNSON: Okay.

DR. LIEBLER: Kurt, the product use would definitely explain that.

DR. KLAASSEN: That's fine. That's fine.

DR. LIEBLER: So, Wilber, what we're referring to is on PDF 67, under the description of the RIFM safety assessment. The second short paragraph.

MR. JOHNSON: Yeah.

DR. LIEBLER: Maybe calculate the range from 125 to 2.5 million, depending on the assumptions of -- and I would take out the numbers, 12 to 30 percent, because it's needlessly confusing. Just say, "depending on assumptions of bioavailability and product use."

DR. BELSITO: "Following dermal application."

MR. JOHNSON: Okay.

DR. LIEBLER: Okay.

DR. BELSITO: Okay. Anything else on this?

MR. JOHNSON: One other thing. Given the use in baby products, as stated in the use

concentration data from the council as well as FDA, should there be any statement relating to any concerns about ingredient use in baby products?

DR. BELSITO: I understand why the Europeans limited it. I think when formulated to be non-irritating -- and there's really not good data that baby skin is necessarily more hyperirritable than adult skin.

DR. KLAASSEN: I think the reason for that is that the main toxicity of salicylates is --

DR. BELSITO: Phototoxic.

DR. KLAASSEN: No, it's actually, as far as death is concerned -- which used to be a major problem in this country. It's not so much anymore, because we have these safety caps. But if you're as old as I am, we used to have to teach this to medical students, because a lot of kids were getting killed every year from aspirin on the kitchen table.

The real problem, for children and adults, is metabolic acidosis and respiratory alkalosis. It is known that children, at that time, were more sensitive to lethality from aspirin. So, that's, I think, where this is kind of going back to; that children are more sensitive to the electrolyte imbalance and the death that can occur from acute exposure.

DR. BELSITO: Okay. So, is anyone concerned about the use in a baby shampoo?

DR. KLAASSEN: No.

DR. LIEBLER: Wilber, I want to call your attention one typo, I think, in the risk assessment on page 56. So the second -- about the seventh line or eighth line down where you have at the top, margin of safety rinse-off peel product equals NOAEL over SED peel product. The third line of that little calculation is 75 mg per kg per day divided by .19. That should be divided by .475. You got that already? You guys got that?

MR. JOHNSON: Yes.

DR. LIEBLER: Okay. Good.

DR. EISENMANN: My question, is that actually needed, that exposure assessment? You have a study where they actually measure -- people use the peel product containing 30 percent Sal. Acid and they measured blood levels. So, I'm not sure why you need to do this calculation, anyway, because you have the real data.

DR. LIEBLER: Did we have that study when we suggested we needed to do this calculation?

DR. EISENMANN: No, you did not.

DR. LIEBLER: Well, okay. Data talks.

DR. EISENMANN: I thought that you could also compare this concentration to -- there's levels of toxic blood levels of Salicylic Acid. So, you could also do -- not just compared to the blood levels when you take an aspirin, which is what they did in the paper, but also to the toxic levels which are later on in the report.

DR. LIEBLER: So the study you're referring to, is that in the document before us?

DR. EISENMANN: It follows right after. In the less conservative estimation -- so it's not an estimation, it's an actual study, where people used the peel formulation and they measured Salicylic Acid in the blood.

DR. BELSITO: Safety margin was 50 to 1.

DR. EISENMANN: And they compared it to -- so the same people, then, took an aspirin and they measured the blood level.

DR. BELSITO: Well, does it hurt to have it all in, since we already did it?

DR. EISENMANN: Well, personally, real data trumps -- especially, since you don't really know --

DR. BELSITO: I don't like that verb.

DR. EISENMANN: Sorry.

DR. LIEBLER: Yeah, we don't use that verb right now.

DR. BELSITO: Real data bests --

DR. EISENMANN: Okay. Real data bests -- if you had data on how much peel a person uses, but this isn't -- they're using how much shower gel you used in place of that.

DR. BELSITO: Right.

DR. EISENMANN: So, the actual study where you have people using the product, as they would use it, and you measure the levels of Salicylic Acid in -- what was it, plasma -- yes. To me is much more appropriate. To say it's a less conservative estimate, well, it's not a less conservative estimate, it's actual --

DR. BELSITO: It's a more realistic estimate.

DR. LIEBLER: It's data.

DR. EISENMANN: It's an actual measurement.

DR. LIEBLER: If we already have these data, we wouldn't have asked for the QRA calculation. I think given that, that's the way we normally operate, working from data. I agree that we probably should delete the

calculation.

DR. BELSITO: Okay.

DR. BERGFELD: And you're inferring, by doing this, you send a message that it was a little bit more concerning than you have stated. Is that why you want to remove it? I understand that you have data, but --

DR. LIEBLER: I didn't understand what you just said. Something about sedated?

DR. BERGFELD: I said, the fact that it would appear with the known data, why would you have to remove it? Does it have the appearance of your worry, without stating it or what?

DR. LIEBLER: Oh, stated. I thought you said sedated, and I was wondering what you were talking about.

DR. BERGFELD: Stated. Doesn't it somewhat support?

DR. LIEBLER: We normally don't have these in if we have data. The argument seems to be that, well, since we did it, it needs to stay in, even after we have data. I certainly wasn't suggesting that I didn't have any faith in the calculation, but it simply an --

DR. BERGFELD: Overkill.

DR. LIEBLER: -- an estimate. Why don't we do that more often when we have data? That's what that suggests to me. Why don't we have these calculations all over the place? We did this because we didn't have data. Now, we have data.

DR. BERGFELD: But you said RIFM does it all the time.

DR. BELSITO: When we don't have data.

DR. LIEBLER: Yeah, right.

DR. BELSITO: Yeah, I mean, I guess the question is, does it set a precedent that whenever there's a concern, even if we have data, we also need to calculate a risk assessment?

DR. SNYDER: I don't want to set that precedent.

DR. BELSITO: I mean, I'm comfortable dropping it.

DR. LIEBLER: I think dropping it when we have sufficient data is more consistent with our practice. RIFM certainly has its practice, but there are a lot of differences.

DR. HELDRETH: Do we want to add something to the discussion section? Saying something about, originally, we requested this when there was lack of data, now that we have the data it's -- so that way, if someone is looking at the record, "why did they not pay any attention to their old risk assessment?" It's explained there.

DR. BELSITO: Sure.

DR. LIEBLER: Yeah. Okay.

DR. BELSITO: I mean, oftentimes, we do add it in the discussion, that we had asked for a risk assessment, and in the interim we got this data.

DR. BERGFELD: Well, you will also say it supported the actual data. I would think it did.

MR. JOHNSON: Dr. Belsito, the only data from that publication by Funk (phonetic) is that statement here. Does any additional information from that publication need to be included? Or is this information as stated sufficient?

DR. BELSITO: I think we should ask that to the toxicologist, not the dermatologist. Dan, Curt, Paul?

DR. LIEBLER: What page, what paragraph were you --

MR. JOHNSON: This is PDF Page 56, and it's the paragraph just below the MOS of 157.

DR. KLAASSEN: In the less conservative estimation?

MR. JOHNSON: Yeah, that's the only information that we have that --

DR. KLAASSEN: That paragraph.

MR. JOHNSON: Yes. Well, just that sentence.

DR. BELSITO: Wilber's asking, I think, is that do more details from that paper need to be included? I think Carl was suggesting yes.

DR. EISENMANN: My suggestion is that you could also compare the results to -- in other places in the report, there's blood concentration of Salicylic Acid that's toxic. So, you'd have a comparison to the aspirin level, and you'd have a comparison to -- and I wrote it in my notes.

DR. SNYDER: Blood levels are down and toxic levels are down.

DR. EISENMANN: Toxic levels -- greater than 300 micrograms per mil is considered toxic; it says that later in the report. There was also a statement that salicylism occurs at greater than 35 milligrams per deciliter, so slightly different units. So you could compare it to that, too, just to show you where you are. So, you're lower on one aspirin, but you're much lower than what's considered toxic too.

MR. JOHNSON: Now, what section of the report should this be included in?

DR. EISENMANN: It can be right in that risk assessment section, where it's at.

DR. BELSITO: Risk assessment.

MR. JOHNSON: Okay. But you'll just only have information from this report in relation to the blood concentration of Salicylic Acid, that is toxic, and the toxic dose that's associated with salicylism?

DR. EISENMANN: Um hmm.

MR. JOHNSON: And that's the only information that should be in the risk assessment section?

DR. BELSITO: As a comparison.

DR. EISENMANN: Well, what you have already is in there --

MR. JOHNSON: So, delete everything else and just add that information, only, in the risk assessment section?

DR. BELSITO: No. I mean, you're going to use the study that was done on the individuals who used the 30 percent rinse-off product. You're going to show the margin of safety. You're going to show the levels that are -- and they're less than what we would get from taking one 325 milligram aspirin, and then you're going to say, and by the way, the level of toxicity for salicylates is this.

DR. BERGFELD: Right.

MR. JOHNSON: When you say show the margin of safety, you're talking about based upon our calculation?

DR. BELSITO: No. You're simply going to get rid of all our calculations. And you're going to get rid of, "In a less than conservative estimation." And you're going to start, "The relative bioavailability of Salicylic Acid following facial application of 30 percent" blah, blah, blah. Continue with all that.

Then second paragraph, in comparison, they looked at individuals who took an aspirin, and this was the level. And then you're going to say, and by the way, the toxic level for salicylate is this.

MR. JOHNSON: Okay.

DR. BELSITO: The question becomes, do we keep the estimates for leave-on? And we do. So, then the rest of it is fine, you're just changing the rinse-off. Okay?

DR. LIEBLER: So, you're going to delete the calculation at the top of PDF page 56, right?

DR. BELSITO: Yeah.

DR. LIEBLER: And then you're also going to delete the lead-in two paragraphs at the bottom of page 55? If you drop that calculation at the top of 56, is there lead-in material, right before it, that you can also delete? I think they can go, right? Did you get that, Wilber? Did you -- are you still thinking about it?

MR. JOHNSON: I have it.

DR. LIEBLER: Oh, you got it. Okay.

DR. BELSITO: Then in the discussion, I think the biggest thing we need to do, in addition to saying why we dropped the risk assessment for the rinse-off, is to explain why we've gotten rid of the photosensitizing sunscreen use. And just point out the new data we have on the actual protective effect of Salicylic Acid.

Okay. Anything else? Okay. Save this baby and move on. So, this has to go out for another review since we've restricted the conclusion. Okay.

December 3-4, 2018 CIR Expert Panel Meeting – Dr. Marks' Team

DR. MARKS: Team, are we ready?

DR. SLAGA: As ready as I'm going to be.

DR. MARKS: We'll start with the draft final amended report on salicylic acid and salicylates. As you recall, these ingredients, 16 of them, were published in 2003. In June of this year, we added additional ingredients. And the panel issued a tentative amended report, with a safe when formulated to be non-irritating conclusion, on salicylic acid and the 18 salicylate ingredients.

Wilbur has updated the report. A margin of safety exposure was accomplished. And, Ron, Ron and Tom, comments? There are lots of updates. Were those okay? Was the margin of safety okay? There was EU limits mentioned in the report. We also have a memo, from this morning, which we just saw. So, I'll let you read that, from Wilbur.

And Wilbur do you want to say anything about this that you supplied this morning, and then also, this accompanying page on categories?

MR. JOHNSON: Just like it says, the International Fragrance Association has established concentration limits for Hexyl Salicylate in different categories of cosmetic products. And you have a handout with those limitations. And also, a handout indicating the product categories -- definitions of the product categories.

DR. MARKS: This is this sheet that, at the top, has 1 percent, category one, 1.3 percent, category 2, et cetera?

MR. JOHNSON: Yes.

DR. MARKS: Yeah, okay. So how is that incorporated in the conclusion when this is so specific and extensive? Is this going to be in the discussion? How do we handle this?

MR. ANSELL: The inclusion of the IFRA?

DR. MARKS: Yes, in other words, our conclusion now is formulated to be non-irritating, a safe conclusion. Wave 2, there were no side effects of the 2 percent salicylic acid cream. And then Wave 3, we had Council comments. Were those Council comments -- that would be after this document. Did that change anything?

DR. SHANK: Well, our margin of safety was based on rinse-off peel products. And I don't see that on any of these categories. I thought the rinse-off peel was the worst case we could consider for margin of safety. I don't see how this changes the margin of safety. It's just more information. I did have a question on the margin of safety calculation on Page 56.

DR. HILL: That's Wave 3 -- or no that's in the --

DR. SHANK: PDF, Page 56.

DR. HILL: -- the main document.

DR. SHANK: And at the very top of the page is a calculation for the systemic exposure dose. And the figure derived was 0.475 mg/kg/day. But in the margin of safety calculation, the systemic exposure dose value is .19. And I don't know where the .19 comes from.

DR. HILL: Yeah. I think that might be a mistake but I'm not sure, because when I divide 75 by .19, I got 396, not 157. So, something is amiss.

DR. SHANK: I didn't do the higher math.

DR. HILL: Well, I just did a back of the envelope with the 75 divided by .2, and said it can't be 157; so then that prompted me to pull out the calculator. But 75 divided by .475 is probably in the neighborhood of 157. So, maybe that just didn't get -- but I don't know.

DR. SHANK: Yeah.

DR. HILL: I can do it --

MR. JOHNSON: I would have to check with Jinqiu, the toxicologist, who did the calculation. But specifically, which value is in question?

MR. SHANK: In the calculation for the MOS. The value inserted there for SED is 0.19, and I don't know where that comes from. And just above that, the SED was calculated to be 0.475.

DR. HELDRETH: Yeah. I think he accidentally transposed the number. You can see the first number in the systemic exposure dose calculation. It was the 0.19. He accidentally carried that down there. But Dr. Hill's right, if you do the math with 75 divided by the .475 it comes out to 157. So, I think it's just a misprint with 0.19 the second time.

DR. MARKS: Thank you.

DR. HILL: Yeah, because that .19 is grams per day if you look, leaving that off; so, that's what

happened.

DR. MARKS: That's Page 56, that would be editorial, the margin of -- pardon?

DR. SHANK: Well, the value of the margin of safety doesn't change.

DR. MARKS: Right, the 157.

DR. SHANK: So, it's okay. We just need to correct the number for the SED. It isn't 0.19, it's 0.475 mg/kg/day.

DR. HILL: Yes.

DR. SHANK: That's in the MOS calculation.

DR. HILL: But I also like the comment that came from the SSC that -- and actually, pretty much the data's in here, it's just a matter of exactly how it's addressed; in that you'd use the plasma concentrations and area end of the curves, and then you can do the direct calculation and compare. And I think the point was the plasma concentrations are available for that peel.

And so, while we the margin of safety calculation, calculating one that relies directly on the relative AUCs, or the CMAX, is actually two different numbers, also makes sense. But that's in here. Right?

DR. SHANK: Yes. And I would say that the conclusion remains safe as used when formulated to be non-irritating.

DR. SLAGA: I agree.

MR. JOHNSON: Just one concern regarding the IFRA limitations. One of the limitations relates to lip products, and there's a 1 percent concentration limit. And please note that Butyloctyl Salicylate is being used in cosmetic products at a much higher concentration, specifically, the 35.9 percent.

DR. SHANK: Quite different.

MR. JOHNSON: Quite different, yes. And it's my understanding that these limitations relate to concern about sensitization.

DR. SHANK: Okay. And they all pertain to Hexyl --

MR. JOHNSON: Hexyl Salicylate?

DR. SHANK: -- Salicylate?

MR. JOHNSON: Yes. I know those are different chemicals, but I was just, you know.

DR. HILL: No, that's very important. Because I'm not sure we fully have captured the absorbability information for the Butyloctyl, for that concentration of use, which I think I flagged the last time. And I thought that was one of the ones that was on my mind in calculating margin of safety.

MR. JOHNSON: We do have log P value for that chemical in Table, I think it's Table 2 --

DR. HILL: Table 2.

MR. JOHNSON: -- for the Butyloctyl Salicylate.

DR. HILL: But the complication there is the ionization, that physiological pH, because the acid is free. So, you really need log D to get a proper picture. Then again, put in a vehicle like a cream and it changes again. What is that leave-on use again? I looked at this, but it's been a while?

MR. JOHNSON: For Butyloctyl, it's 35.9 percent.

DR. HILL: But what's the use? It says mucous membrane, that sort of suggests lips.

DR. SHANK: Lipstick, isn't it? It's used in the lipstick?

MR. JOHNSON: Yeah, it is used in lipstick at 35.9 percent.

DR. HILL: Hence, the incidental ingestion, which, again, incidental, I'm not worried about that. Yeah, so the body area -- it's mucous -- but the body area in a lipstick would be very small. If you did a cumulative estimate for that, which due diligence suggests we really ought to do; and you could use -- is it IFRA that has -- well, the European Union, in general, they have surface areas that one can use.

But I don't guess we have any dermal penetration that would be relevant to lips in here. Yes, all we've got is Methyl Salicylate, and that bugged me the whole time I looked at this. And so, log P, that would be the free acid, and again sitting on lips. It's not really in aqueous solution, it's the free acid that's in there. Log P of 6 puts it in the sweet spot for transdermal delivery, so that's interesting.

DR. MARKS: Enough, Ron Hill, that you'd want to change the final amended conclusion, safe when formulated to be non-irritating?

DR. HILL: No, because I don't think you could get enough salicylate into the system fast enough by that route, from a lipstick, applied a few times a day maximally. But still, you'd think we should have a margin calculation, given that high percentage of use.

DR. MARKS: Ron Shank? I mean if we need another margin of safety calculation, obviously, we can't move forward. We would have to want to see that before we issue a final conclusion.

DR. HILL: Well, we could do it between now and tomorrow, and see what we come up with. I

don't think it's a hard calculation.

DR. SHANK: I thought we were using the 30 percent peel? It would be a lot greater impact on the skin, and 39 percent in a lipstick.

DR. HILL: But the substance in the peel is what?

DR. SLAGA: And then we have a limited area.

DR. HILL: What's the substance in the peel?

DR. SHANK: Salicylic acid.

DR. MARKS: Salicylic acid.

DR. HILL: Yeah. So, that's going to be a very different absorption profile than Butyloctyl Salicylate. Salicylic acid is not particularly lipophilic. Yeah, a smaller molecular weight, but I doubt very dermally absorbable. I mean, we've looked at that, so we know that answer. But by comparison, these lipophilic esters would get across skin barrier, or at least into the skin, where there might or might not be esterases in the lips that will take that out rapidly, or not, in humans.

DR. MARKS: Tom?

DR. SLAGA: I don't think we need another calculation. I think what Ron Shank is saying is correct, that we have it for the skin. And I think, we take into consideration that they are less on the lips, so even if it wasn't --

DR. MARKS: Well, why don't we -- and then, Ron Shank, I hear you feel comfortable with the margin of safety calculation we have and the conclusion. Ron Hill, we could see, Wilbur, see if you have a margin of safety, but you can certainly bring that up tomorrow, Ron Hill.

DR. HILL: I just feel like there have got to be available numbers for if we smear lipsticks on a fairly large person's lips, how many milligrams of lipstick, at 36 percent, and how much of that is Butyloctyl Salicylate? We've got the surface area, the lips, then make a conservative assumption; and I think you'll see it's not going to get into the system at a level of concern.

Even if you put the lipstick on ten times a day -- which people don't. It seems to like, again, a due diligence or credibility thing, I think would be the better way to put it, by having that in there. I'm not suggesting we should have to delay the process. I feel like that number could be produced by tomorrow, if somebody feels inclined to do it.

DR.MARKS: Well, that would be Jinqiu who did this. He's going to be correcting that. I'll mention that tomorrow. Our team will be seconding the Belsito's motion. Presumably, it would be safe when formulated to be non-irritating. I'll mention that we need to edit the margin of safety calculation, on Page 56, that the SED is 0.475 mg/kg/day, producing a margin of safety of 157 as shown. So, that change will be made.

And then, Ron Hill, I'll mention if you want to comment about another margin of safety for lip exposure to the Butyloctyl Salicylate at 35.9 percent use. And I think, was there anything from Wave 3 in the council's comments that we needed to react to?

DR. SHANK: Not for me.

DR. MARKS: Okay, okay.

DR. ANSELL: We do want to raise a concern that the Hexyl Salicylate, which is the subject of the IFRA conclusions, this is essentially, exclusively a fragrance ingredient, and we always run into a little problem with jurisdiction. But if we choose to continue to carry it forward, we think the IFRA conclusion should be included but in the cosmetic use section.

MR. JOHNSON: I might mention that, according to the dictionary, there is another function for the Hexyl Salicylate, other than just fragrance material.

DR. HELDRETH: Right, skin conditioning agent.

MR. JOHNSON: Yeah, it's a skin conditioning agent.

DR. ANSELL: The dictionary, itself, is not a normative reference for use.

DR. HILL: Well, it shows a maximum use in our table of .12 percent for leave-on, and .52 for rinse-off, for Hexyl Salicylate; not Ethylhexyl, but Hexyl. We don't really have a problem, from that point of view. And if it's used in cosmetic products -- no matter it's used in a fragrance ingredient or not. If the use in the cosmetic product is not fragrance, then I don't see any jurisdictional issue.

If we were exceeding the limits that IFRA was setting, then I could -- I mean, I think we may still need to incorporate that information, that they've set those limits, somehow in the report. Where, was I thought what we started this discussion with, and we never answered it. In the discussion section, or would it be up at the front in the non-cosmetic use? I think non-cosmetic use if it's a fragrance. I mean, I don't know.

DR. ANSELL: Yeah, our suggestion is to put it in the use section.

DR. MARKS: In the use section.

DR. HILL: And you could put those limits in there, just in the text, I think.

DR. ANSELL: Yeah.

MR. JOHNSON: Dr. Marks.

DR. MARKS: Yes.

MR. JOHNSON: Just one thing. We talked about the concern about percutaneous absorption, you know, through the lip. Are there any concerns about incidental ingestion?

DR. HILL: I don't. Because under those circumstances we would know intact Butyloctyl would reach any place where it would be absorbed in any other way than salicylate, and the levels would be far lower. That wouldn't be worth doing the calculation.

I had a couple of other things, but I wanted to make sure -- just a general comment from me is, again, the Capryloyl is structurally different; and there's information I asked about, in the last go-round, that I don't think I need to repeat again here, that I still think due diligence suggests one ought to have. So, I have a problem with that particular compound, myself.

I wondered what we're doing, with not just this ingredient but all of them with things about inhalation, given our state of evolution on our aerosols work? I don't think we were suggesting we should table all of these ingredients so we can get the new aerosol language in there. But yet, I wondered how we planned -- because you know how I feel about this stuff about the -- I could go to Page 41 and find it. But I wrote a note here, "Please consider moving that to the discussion." Some of the language related to that to discussion, related to particle size, whatever, and then whatever we end up landing on.

MR. JOHNSON: Well, Dr. Hill, the last paragraph of the discussion does address inhalation exposure.

DR. HILL: Right, it does. But then the question is why do we need -- here's the language, let me go to Page 41 of the PDF. The language says, "in practice, 95 to 99 percent of the droplets/particles released from cosmetics sprays going down in lungs to any appreciable amount." And then again, "conservative estimates of inhalation exposures." All of that.

I mean, that's discussion, and it's been discussion since I've started reading these. And I wonder why this goes right up front here? You just say, they're used in these sprays. Then down further, we may or may not have aerosol inhalation toxicology. When you get to the discussion section you either say, here's what we have on inhalation toxicology, or we don't have it, and we think we don't need because here's why.

But it always bugs me, it always is glaring, when you have it right up here in the use section; and we get into the practice 95 to 99 percent, blah, blah. And then conservative estimates. Those are not introductory or use comments, those are discussion of why the inhalation toxicology is or isn't important, and to what extent, to me.

And then there was always the concern, well, we don't put references in the discussion section. And I say every journal I've ever published in, you put references in the discussion section, so what's the problem here?

DR. MARKS: Tom, Ron, any comments?

DR. SHANK: No.

DR. MARKS: It's okay the way it is.

MR. SLAGA: Right.

DR. SHANK: For me, yes.

DR. MARKS: Okay. So, again, I'll reiterate we'll be seconding a motion. Presumably, it'll be a final amended report with a conclusion, safe when formulated in the non-irritating. We edit the margin of safety calculation on Page 56. I presume the Belsito team will catch this, but if not, I'll mention that the SED is really .475 mg/kg/day in the calculation.

I'll mention, Ron Hill, about another MOS for lip exposure. Is that necessary at the 35.9 percent concentration of Butyloctyl Salicylate? And the IFRA consolation limits in the memo, which Wilbur just gave us, will be in the cosmetic use section for Hexyl Salicylate.

DR. HILL: Two more things. One is just a general comment. On Page 43, there's dermal penetration study and it has three women skin samples in the formulation; and it gives an amount in microgram per cubic centimeters was applied to the skin, in so much time.

My question that I wrote in here, "But what was the concentration?" Because amount doesn't tell you anything about diffusion rate. Concentration drives diffusion rate. The higher the concentration, the higher the mass transfer rate, plain and simple. So, we always need to know, when we write up dermal penetration studies, and certain surface areas. Surface area is always important to know because the mass transfer rate is directly proportional to surface area. The other important factor is concentration. It didn't capture, and so that might be

available.

And then the last thing is, on the Capryloyl, which again is problematic for me because of the structural dissimilarity and the lack of information about is this really a souped-up aspirin? We put to bed the sensitization, in part, by saying the contamination with a 3-capryloyl isomer is the likely isomer. And I wanted to know is that conjecture added by us; or if it was conjecture in the reference report, and on what basis does anybody actually believe this?

MR. JOHNSON: Where are you reading from?

DR. HILL: Page 65 is the contamination with the 3-capryloyl. And I'm not sure I know what that is, because 3 is kind of ambiguous in salicylic acid, but I think I know what it is. And that would be acylation on the aromatic ring if that's what they're asserting. I'm assuming that's not something we added, it was something drawn from the literature reference; but I wondered on what basis they made that conclusion.

MR. JOHNSON: Which ingredient and which paragraph?

DR. HILL: All right, let me get there. I'm sorry. It should be Page 65, I thought. Under sensitization, it would be -- yeah, okay, case reports. And I agree that it stated that Capryloyl --

DR. MARKS: Is it the Capryloyl Salicylic acid, the case reported of that female patient you're talking about?

DR. HILL: Yes, yes, sir.

DR. MARKS: To me, a case report is a case report, it's an alert. Unless I see multiple followed up, a mini-epidemic, I take it as is, it's sensitized in this case, and kind of leave it at that.

DR. HILL: I agree with you, but my question was, where did that statement about the 3-capryloyl come from? I want to make sure that it's taken from the reference and not our suggestion. Because if it's coming from us, there's a credibility issue.

DR. MARKS: Yeah. No, I'm sure it's from the reference.

DR. HILL: And if it is coming from Reference 92, which I didn't look to verify, I wondered where they got that? But it doesn't matter. I think it needs to be written to indicate this was the authors' of that articles' conjecture, and not ours.

MR. JOHNSON: Okay. So, I should revise it to indicate that's the authors' opinion?

DR. HILL: Just -- then that would be editorial.

MR. JOHNSON: Okay.

DR. MARKS: Any other comments? If not, we'll move on to Vinylpyrrolidone Polymers.

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DR. BELSITO: So, this came up as a re-review at the September meeting, and we decided to reopen it to add three additional ingredients: Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate. We looked at all the material. There are some points in the discussion that I'll get to later, but in general our conclusion was safe as used when formulated to be non-irritating and non-sensitizing; and non-sensitizing, you could use QRA or other methodologies.

DR. MARKS: Interesting, yeah. I'll second that. I'd be interested in the reasoning with the non-sensitizing, Don. We went just not irritating.

DR. BELSITO: Well, because IFRA has limits on hexyl cinnamate, and there's evidence of sensitization -- or Hexyl Salicylate. There's some evidence of sensitization there. So, we need to respect, I think, those limits and what IFRA has found.

DR. BERGFELD: And that is included as a reference here in the document?

DR. BELSITO: Yeah, the data for IFRA is in the document.

DR. BERGFELD: Thank you. Any other comments? Okay. Could we take the vote first and then go to the discussion?

DR. MARKS: Second.

DR. BERGFELD: All those in favor indicate by raising your hand. It's safe. Okay. It's unanimous? Are you voting yes or no right now?

DR. HILL: We aren't discuss -- you said go to the discussion.

DR. BERGFELD: We're going to go to the discussion afterwards, because there are discussant points too.

DR. HILL: Okay. All right.

DR. BERGFELD: All right.

DR. HILL: I thought we usually discuss before we vote.

DR. BERGFELD: Oh, no.

DR. HILL: Oh -- I'm sorry. I thought we usually discuss before we vote and then --

DR. BERGFELD: We're going to the discussion now. Thank you. The discussion?

DR. BELSITO: So, first we had originally asked for a risk assessment for both rinse-off and leave-on products. We actually got actual data on rinse-off products. And my panel felt that we could drop the risk assessment for the rinse-off since we have the actual data, and data bests, a risk assumption. We would keep the risk assumption for the leave-ons; and then, just to point out further in that risk assumption, there was the mention of what happens when you take one aspirin and a big concentration of salicylate. It was recommended that we also add in a short sentence as to what the actual toxic levels for salicylate would be, to point out exactly how good our margin of safety is. There was one comment.

DR. BERGFELD: Mark's team?

DR. MARKS: Our edits included, on page 56, the margin of safety calculations. I assume you wanted to keep that. The SED in that was really 0.475 milligrams per kilo per day, that produces a margin of safety of 157 as shown. So, there's a typo in that formula.

DR. BELSITO: Yeah, we picked that up, but we're dropping on that because that's for rinse-offs, and we actually have hard data for rinse-offs now. And we felt that the hard data is superior to a risk assessment.

DR. BERGFELD: Ron Shank, what do you think?

DR. SHANK: It's okay. It gives more confidence in the risk assessment. And now we have the hard data that support the risk assessment. But if you don't want, take it out, I don't object.

DR. BELSITO: Well, we were just concerned that it may set a precedent that we have hard data and then we also do a risk assessment on it. If we actually have the data, then there's no need to do the risk assessment.

DR. BERGFELD: Ron Hill?

DR. HILL: Just for clarification, that was the peel, correct?

DR. SHANK: Rinse-off peel.

DR. BELSITO: Rinse-off, yes.

DR. HILL: Rinse-off, peel? Yeah, okay. Because that's where we had serum levels and exposure estimates.

DR. BELSITO: Exactly.

DR. HILL: AUCs, all of that, yeah.

DR. BERGFELD: Paul? Dan? Curt?

DR. KLAASSEN: Fine.

DR. BELSITO: Okay. Another discussion point? Are we done with that?

DR. BERGFELD: Please.

DR. BELSITO: Previously, we had restricted this and asked that a warning be put on the label for sun protection. We now have data that that is not an issue. So, I think, in the discussion, we need to point out why we've dropped that restriction for Salicylic Acid.

MR. JOHNSON: That's already in the discussion, Dr. Belsito. It's there.

DR. BELSITO: Yeah.

DR. BERGFELD: Okay. Ron Hill?

DR. HILL: I expressed concern about the capryloyl ester last time, and I still have the concern. I am encouraged that there's only one percent maximum use in leave-ons, but I still think I would want to see whether it is, or is not, a direct cyclooxygenase inhibitor. I still feel uncomfortable with that particular one.

DR. BERGFELD: Okay. Dan.

DR. LIEBLER: So, I remember our discussion last time, Ron, about that. I talked my colleague Larry Marnett; he's kind of one of the foremost biochemistry experts on cyclooxygenase inhibition. He said that the longer chain acyl derivatives have increasingly lower activity as inhibitors, so acetyl was the most. And then a longer chain one may not even be able to access the active site very well. The other thing is, I actually found a reference we could add to the report that actually compared platelet aggregation efficacy up to, like, butyl. But it's consistent with what Larry mentioned to me. So, I think that the concern about the capryloyl is mitigated by that.

DR. HILL: Okay, I'm good, too, then. That was my suspicion, but I didn't have any hard documentation. That sounds right in terms of what's known about the SAR, so, I'm good.

DR. BERGFELD: So, have you added that to the --

DR. LIEBLER: So, Wilbur, I'll email you the reference.

MR. JOHNSON: Okay.

DR. BERGFELD: Okay. Thank you.

DR. HILL: Yeah, if we could add that, that would be great.

DR. BERGFELD: Any other discussion or comments or editorial comments? Wilber?

DR. MARKS: Well, I was going to ask, Ron Hill, yesterday you brought the question of whether another margin of safety should be calculated for the lip exposure of 35.9 percent of Butyloctyl Salicylate. Are you still concerned about that, Ron Hill? I'd be interested in what the Belsito team feels about it.

DR. HILL: I feel like it's going to show us that everything is fine. Just that it's a high concentration, 36 percent, if I'm not mistaken, almost in the leave-on in lip. But the surface area is small. It just feels like -- and so, total systemic exposure from that has got to be really small because the rate of access to the system should be low. I mean, I slept on this since then. I don't think it's crucial.

DR. HELDRETH: Overnight, though, Jinqiu actually did a MOS calculation for that and it was well over a hundred.

DR. HILL: Well over a hundred. That would have been my guess. That's great.

DR. BERGFELD: Can that be added?

DR. HELDRETH: Absolutely.

MR. JOHNSON: So does that need to be added to the safety assessment, that risk assessment?

DR. BELSITO: Yes.

MR. JOHNSON: One other concern. On PDF Page 60, we have irritation and sensitization data. The discussion doesn't contain any information relating to irritation or sensitization potential; so, what information should be included in the discussion to support the conclusion?

DR. BERGFELD: Don?

DR. BELSITO: I think just a summary of that irritation and sensitization data. And that we realize that irritation is a very variable phenomenon, depending upon product formulation; so that we really can't really give a percentage number. Sensitization is less variable; and that's why I said that it should be assessed by methodologies, such as QRA or other excepted methodologies, since I can't give a specific number for that.

DR. BERGFELD: Okay.

DR. MARKS: Don, you were going to include the IFRA concentration limits, cosmetic use for Hexyl Salicylate in the use section, or not? You had mentioned that was one of the tipping points for having the sensitization portion of the conclusion.

DR. BELSITO: I don't know where that appeared. But, yeah, I mean it could be put into the cosmetic use section that there's a limit that's been set.

DR. BERGFELD: Bart has whispered to me that this will have to go out again because of the

change in the conclusion; so it will go out for 60 days.

DR. BELSITO: Yes.

DR. BERGFELD: And we've already voted on this, so we can move forward then to the next group. The next group of reports advancing, these are at various levels. The first one is Dr. Marks and the lactate salts.

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DR. LIEBLER: Just a second there, Don. I'm sorry. Are we doing Capryloyl Salicylic Acid?

DR. BELSITO: Oh, I skipped that. Oh, sorry.

DR. LIEBLER: Yes.

DR. BELSITO: Okay. So this is also the first time we're looking at this, sort of. It was split out from the salicylic acid report because it's a ketone and not an ester. So, all of that data has been brought over into this document. Just again, looking at the document itself, under impurities, I didn't like the phrase "highly plausible contaminant." Dan, what do you think about that? Paul?

DR. LIEBLER: I think it's either measured or detected, or it's not. So, it should be mentioned if it's been measured or detected and not mentioned otherwise. Because otherwise, the reader has no way to interpret that. Is it there or not?

DR. BELSITO: So, delete it if it's not been measured or detected?

DR. LIEBLER: Right. And then that leaves us with nothing on impurities; no characterization of degree of purity. I think we should be able to do better than that, even if it's just our usual, this ingredient has been reported to be 98 percent pure, 99 percent pure or whatever. But can we get some accompanying data sheet that might provide a little bit more info?

DR. BELSITO: So, one of our data needs for this is impurities?

DR. KLAASSEN: Yes.

DR. BELSITO: Then, on PDF page 10, the paragraph above Toxicokinetic Studies, it says, however, the baring -- I presume that's bearing, B-E, not B-A -- of these raw material particle sizes on the particle sizes of the final consumer product formulations is not clear.

I didn't really follow that. So the particle size as a raw material, and then you're saying that doesn't tell us what it is in the final consumer preparation. Do we think this will agglomerate for any reason?

MS. EISENMANN: Well, it's mixed with other things. So I'm not sure. Since it's mixed with other things in the product, I don't think that usually the -- see, I wouldn't put the particle size of the ingredient under cosmetic use.

DR. BELSITO: Right.

MS. EISENMANN: I would put it under chemistry or physical description and move it. And then you don't necessarily have to have that additional statement.

DR. BELSITO: Right. Okay.

DR. LIEBLER: Depending on the nature of the formulation, I think that this ingredient would be dissolved and fully dispersed. It's not really a particle like we would think of silica and things like that. So, I think that description is probably a misrepresentation of the form of this. Unless it was in a purely aqueous type solution, it would probably be dissolved and fully dispersed.

And as a skin conditioning agent, if it was purely aqueous, this might not be very soluble anyway. Well, it would be somewhat soluble I guess, with a carboxylate. But I don't see this forming some particle that would need to be accounted for in the way we usually worry about particles, particle sizes.

MR. JOHNSON: So, just move the first sentence in that paragraph to the chemistry section and delete the second sentence?

DR. BELSITO: Yes.

MR. JOHNSON: Okay.

DR. LIEBLER: Yep.

DR. KLAASSEN: Do you even want the first sentence kept?

DR. BELSITO: In the chemistry section.

DR. KLAASSEN: Yeah, but even that. I guess it would be my suggestion to just remove this 100 percent, but I don't feel strongly.

DR. LIEBLER: Yeah. I would have no problem with that actually, Curt.

DR. BELSITO: So, you want to delete that completely?

DR. KLAASSEN: Yeah. I don't think it helps anybody.

DR. LIEBLER: Yep.

DR. KLAASSEN: Causes more confusion than help.

DR. BELSITO: But then, do we -- I mean, we do have some information on particle size. Again, we could be criticized for not including it.

DR. LIEBLER: Well, I could honestly go either way. You could take just that particle size sentence and put it in under Chemical and Physical Properties, right before the last sentence in Chemical and

Physical Properties.

DR. BELSITO: I'd be happier with that.

DR. KLAASSEN: Fine.

MS. EISENMANN: Wilbur, you also have that sentence in the paragraph above the last paragraph in the cosmetic use section, so it has to be moved from there too.

MR. JOHNSON: Where is that again?

MS. EISENMANN: In the cosmetic use section.

MR. JOHNSON: Yes, that's what I was --

MS. EISENMANN: Because it's in there twice.

MR. JOHNSON: Okay. Where's the other location at?

MS. EISENMANN: It's in the fourth and fifth paragraphs.

MR. JOHNSON: Okay. Thank you.

MS. BURNETT: It's the one about five rows up.

MR. JOHNSON: I see. Thank you.

DR. LIEBLER: Just repeated by accident, so I'd just delete it entirely from that paragraph.

DR. BELSITO: Okay. On PDF page 11, right at the top, it says, based on this method, 17.1 percent of the applied test material was found in the stratum corneum, versus 9.7 percent of salicylic acid applied.

I don't understand what you're trying to say there. Was the Capryloyl Salicylic Acid and salicylic acid both applied? I don't --

DR. KLAASSEN: I assume there was two different experiments. In one, they used this ketone compound, and the other was just plain salicylic acid.

DR. BELSITO: But it doesn't say that. It says the skin penetration of Capryloyl Salicylic Acid was assessed in the standard stripped skin method. And then it says --

DR. LIEBLER: I think you're just going to need to reconsult that reference and see if you've missed something there.

MS. FIUME: Um-hm. Because it does say the sal acid was in the same vehicle, but the details just need to be brought over.

DR. BELSITO: Right. Okay. And then in vitro, it was clastogenic with but not without metabolic activation. I always have problems with these studies. So that when you see in effect with but not without, you don't worry about it? Is that true?

DR. KLAASSEN: No.

DR. BELSITO: No?

DR. KLAASSEN: No. You're, I think, equally concerned. But I think --

DR. BELSITO: This is page 14.

DR. KLAASSEN: Yeah. I was just looking for it.

DR. LIEBLER: It was clastogenic in the Chinese hamster ovary cell in vitro with metabolic activation. But it was clean in two follow-up in vivo clastogenesis tests.

DR. BELSITO: Okay. So you're fine?

DR. LIEBLER: I am.

DR. KLAASSEN: Yes.

DR. BELSITO: Okay. Does that go in the discussion? Or we just ignore it since the in vivos were clean?

DR. LIEBLER: You can mention it in the discussion. Since there's no carcinogenicity data, we should be clear on our reasoning for why we're not asking for it. And I think we're -- it's got no structure alerts and it's fine on the in vivo clastogenicity. It was also a negative Ames, with and without metabolic activation.

MR. JOHNSON: So you're not concerned about genotoxicity or clastogenicity based upon the two negative in vivo clastogenicity assays and the negative Ames test with and without metabolic activation?

DR. LIEBLER: Correct.

MR. JOHNSON: Okay. Thank you.

DR. BELSITO: And then, the sensitization and irritation, we have two HRIPTs with 106 in one and 105 and the other at .5 percent, and they were clean. However, the guinea pig maximization study would indicate that it does have the hazard of a sensitizer.

So, while I think we probably have the information we need, we should try and calculate a NESIL from that and make sure that the use concentrations are either acceptable so we can say safe as used, or whether we need to say formulated to be non-sensitizing.

Then, on page 16 under Case Reports -- you have those two case reports of individuals with

reactions to Capryloyl Salicylic Acid. Then, in the third paragraph, you say, "In a letter to the editor on the preceding two case reports, the author" -- I think the author is not the author of the case reports, so it should clarify that.

I wouldn't say the author. I would say something like, in a letter to the editor on the preceding reports, it was suggested that Capryloyl Salicylic Acid is unlikely to be significantly allergenic and cause contact allergy. The structural isomer -- so, you can include that, but I just would get rid of "the author," because it sort of makes you think that it was the author of the case reports who then came back and said, oh, well, I was wrong.

DR. LIEBLER: Wilbur, you could just begin that sentence, "A letter to the editor."

MS. FIUME: Stated.

DR. LIEBLER: Stated.

DR. BELSITO: In their letter. Yeah. Okay. So, basically, we need just impurities.

DR. LIEBLER: Yeah.

DR. BELSITO: Otherwise, safe as used when formulated to be non-sensitizing, using methods such as a QRA, and non-irritating.

DR. LIEBLER: Right.

DR. BELSITO: Or if the QRA clears all current use levels, then just safe as used.

MR. JOHNSON: Dr. Belsito, there's no concern about irritation potential?

DR. BELSITO: Yeah. Irritation.

MR. JOHNSON: Irritation and sensitization?

DR. BELSITO: Yeah. But what I'm saying is that we could say safe as used when formulated to be non-irritating, if the QRA clears all the current use concentrations. And we don't need to mention sensitization.

I mean, we have two HRIPTs which are clean, but the guinea pig maximization test would suggest that this does have a sensitization hazard. We just don't know whether the current use concentrations mitigate that hazard. Okay? So, essentially impurities and run a QRA.

June 6-7, 2019 CIR Expert Panel Meeting – Dr. Marks' Team

DR. MARKS: Next is Capryloyl Salicylic Acid. This is what you were talking about. You were just one group of ingredients ahead.

DR. BERGFELD: I know. I saw that. Sorry about that.

DR. MARKS: You were anxious to get down through this list. So this is a draft amended report on Capryloyl Salicylic Acid. Is that how you say the first word there?

MR. JOHNSON: Capryloyl, I think. Some say capryl --

DR. MARKS: Thank you, Wilbur. Well, I'm going to be seconding it, so I won't have to pronounce it tomorrow morning.

Any rate, we have the one ingredient which was separated from the previous reports of the esters. That was the ketone you were talking about, so it is one less.

And why do I have tentative amended report? I have safe when formulated to be non-irritating and non-sensitizing based on a QRA. There was irritation in animals and in the HRIPT, as well as the ocular irritation. So there's no question these are irritants.

Then there was sensitization in animals in the guinea pig max. The HRIPT was non-sensitizing. But again, based now on the guinea pig max being an alert, even though the HRIPT was non-sensitizing, I think we've evolved into -- if there's any alert for sensitization, we should add in the conclusion non-sensitizing based on QRA.

DR. SLAGA: Right.

DR. MARKS: And Ron, probably in the future, we'll also add another -- that it's formulated to be non-toxic. But we haven't gotten there yet.

DR. BERGFELD: We are peeling it down to that, though, aren't we?

DR. MARKS: I know. But any rate, does that --

DR. BERGFELD: Do you think it's important to do this?

DR. MARKS: That's how I formulate it. Does that sound good to you guys?

DR. SLAGA: Yes.

DR. MARKS: Non-irritating and non-sensitizing.

DR. SHANK: The sensitization data were negative.

DR. MARKS: The HRIPT is, but the guinea pig is positive.

DR. SLAGA: There's both positive and negative on irritation, as well as sensitization.

DR. BERGFELD: Do you think in your presentation you have to say this is the third amended to this?

DR. MARKS: Oh, yeah. I don't know that we need to say it's the third amended. I don't know that we have to -- this one is based on removing -- so we have 18 ingredients -- 18 esters, minus the ketone in the past. So I can go -- what page is that, with the sensitization? But I'm sure -- what I was doing, Ron, is based on how we've been going over the last year or so, whenever we have a sensitization alert.

And Don was very specific about HRIPT is not totally predictable. It helps us. But I think Don is very -- I'll put this in quotes, "sensitized" from MCI/MI. No pun intended. So he wants to be overly cautious, and that's why he's added the QRA in these. We'll see what the other team -- I'll be seconding it. But that's the direction I would take.

I hear you. In the past, if the HRIPT was non-sensitizing, we would say, okay, it's fine. We don't have to worry about sensitization.

DR. BERGFELD: Has anybody written a paper on that?

DR. MARKS: About the QRA?

DR. BERGFELD: No, about the HRIPT and the fact it's not totally predictive.

DR. MARKS: Not that I'm aware of. That's an interesting proposal.

DR. SHANK: So if we had that plus the lymph node assay, the two together, would you be happy?

DR. MARKS: If it were negative in both?

DR. SHANK: Yes.

DR. MARKS: I guess, then, you'd say are the guinea pigs lying. You know, how do we deal with these mixed results?

DR. SHANK: Okay.

DR. MARKS: For me, if you're being ultraconservative, you take Don's tactic, which I agree

with. You say formulated to be non-sensitizing. Then it really does make the formulator, I would think, think more about, "Okay. Could I sensitize people in this use?"

DR. SHANK: Okay. Put you give him an out by putting in the QRA caveat?

DR. MARKS: Right.

DR. SHANK: Okay. Dr. Hill had some other issues.

DR. MARKS: Okay.

DR. ANSELL: Before we leave the QRA, we want to make sure that the language is not obligatory. It's permissive when formulated to be non-sensitizing. And you can use QRA.

DR. MARKS: Yeah. I think the way Don has it, based on QRA or other methodologies.

DR. ANSELL: Right. Right.

DR. BERGFELD: Do you think you would put that in the discussion, or you'd put it in the line conclusion?

DR. ANSELL: Well, Jim's suggested wording was non-sensitizing based on QRA. And we just want to make sure that QRA --

DR. MARKS: Well taken.

DR. SHANK: Non-sensitizing, which can be determined by a QRA. It doesn't say "based on." It says it "can be determined."

DR. BERGFELD: I'm just wondering if that's appropriate for a conclusion -- non-sensitizing. But if you take care of it in your discussion, that you can use the QRA, it seems to me that would be more appropriate.

DR. SHANK: Okay.

DR. BERGFELD: Just my opinion.

DR. SHANK: We have used it in the past.

DR. BERGFELD: We're just recently moving it to the conclusion. It's just a couple times now. We've done it two or three times today.

DR. MARKS: Oh, yeah.

DR. BERGFELD: It seemed to me non-sensitizing would do for the conclusion.

DR. ANSELL: No, I think that's very reasonable. In fact, what staff may want to do is -- they're not called boilerplates anymore. They're called guidances or --

MS. FIUME: Guidance documents.

DR. ANSELL: To talk about how sensitization can be --

DR. BERGFELD: We ever have a chance at looking at all those?

MS. FIUME: Yes, but the ones that really need updating need a toxicologist right now.

DR. MARKS: Well taken, Wilma. I always like less is more, sometimes. And so if you just put non-irritating and non-sensitizing, then in the discussion, you clarify what you mean. I actually do like the idea of also having a boilerplate for both of those, potentially, but certainly for sensitizing.

DR. SHANK: I'm a little uneasy about putting the burden on the formulator for sensitization. To say non-irritating is pretty good because a lot of things tested date are irritant, but in formulation are not. That's not necessarily true for sensitizers.

So if you tell the formulator, "Just formulate it to be non-sensitizing," we're not doing our job, are we? Even with the QRA out --

DR. MARKS: Well, or other methodology, as Jay correctly pointed out.

DR. SHANK: Okay. But if you say safe conclusion when formulated to be non-sensitizing, period --

DR. BERGFELD: So you're voting to put the QRA into the conclusion, or thereabouts, other methods?

DR. SHANK: Correct. Or we can discuss it tomorrow.

DR. MARKS: I think Don was the first one that, I think, came up with that terminology. I'd be surprised if he changes. But then again -- one of the things it does is it makes it clear in the conclusion how you're going to deal with the issue of non-sensitizing.

MR. JOHNSON: Dr. Marks, the other team recommended calculating a NESIL based upon the positive guinea pig sensitization test data. I just thought I'd throw that in.

DR. MARKS: We'll hear that tomorrow. I think that's fine.

DR. ANSELL: I think we wanted to recognize the QRA was an acceptable method of determining sensitization. But I think what we're finding, particularly with the development of AOPs, adverse outcome pathways, we're starting to look at a molecular level of the cause of sensitization. And I think, at some

point, we're going to want to start relying on those methodologies as well.

So now, we're going to say HRIPT or QRA or at least a combination of OECD 1413, 1414(a). I think we wanted to -- and that's why I liked Wilma's discussion. I think within the discussion we can say this is a method we consider to be reliable, but we're going to have more reliable methods as time goes on.

And it's not only going to be cancer. It's not only going to be cancer endpoints, but reproductive endpoints. And I think we're very far advanced in sensitization, understanding it at a molecular level and the ability to predict whether materials would be sensitizers based on omics.

DR. BERGFELD: Based on what?

DR. ANSELL: Genomics.

DR. SLAGA: Omics of any type.

DR. BERGFELD: Okay.

DR. MARKS: So thanks for giving us a little prep for tomorrow, Wilbur. But it's interesting. Do they -- and you can share this or not -- did they want to include that in the discussion and postpone issuing a tentative amended report? Because this is tentative amended, so we're going to have another look at it. They must have had a conclusion.

MR. JOHNSON: Basically, with that information, they would be able to determine whether or not the use concentrations would cause sensitization based upon that calculation. With that in mind, it may not be necessary to say formulated to be non-sensitizing -- based upon those results. So that's sort of where they left it.

DR. BERGFELD: So they would wait for that tabulation?

DR. MARKS: They have to have a conclusion if you're going to move forward to a draft final. Or are they going to, quote/unquote, "table it" until we get the NESIL?

MS. FIUME: It's the first time it's truly being reviewed, so it can go out as an insufficient data announcement, as well. Because, to clear up how it's gone through, when it was originally included in the Salicylic Acid report that was published back in 2003 or whatever it was, it was incorrectly classified. And the structure was incorrect.

So this is the first time this ingredient, as being correctly identified, is being reviewed. But because it had been in the Salicylic Acid report, it has to be an amended report because there is a conclusion out there. And it was pulled out of the Salicylic Acid document that just went through and is being reviewed by itself.

So because it needs a new conclusion, because the existing conclusion wasn't correct for what we now know this ingredient to be, it can go through the entire process. It can go out as an insufficient data announcement. It's like a new ingredient.

MR. JOHNSON: As a matter of fact, that is one of the items in the other team's insufficient data announcement.

DR. MARKS: Okay.

DR. SHANK: And Dr. Hill's? He had a fair amount of data needs. One is on phototoxicity. He says UV absorbance surely will occur. Therefore, there's a need for phototoxicity data.

His second need is a way to handle the level of 3-Capryloyl impurity in commercial supplies, and whether this is the agent that causes sensitization.

And then, he had another issue, which is not a data need. And that's their references to comedolytic activity.

MR. JOHNSON: What kind of activity?

DR. SHANK: Comedolytic.

DR. BERGFELD: Acne.

DR. SHANK: Comedolytic?

DR. MARKS: But he says lytic, so if anything --

DR. BERGFELD: It clears it out.

DR. MARKS: Yeah. It does and proves it. But that's not surprising.

DR. BERGFELD: All acids.

DR. SHANK: Okay. He thought there needed to be more information on that captured in the report.

MR. JOHNSON: Comedolytic activity?

DR. SHANK: Yes.

MR. JOHNSON: Okay.

DR. MARKS: What was the second one, which he thinks may be the sensitizer? He wants more phototoxic.

DR. SHANK: I'll quote. "We need better handle on the level of 3-Capryloyl impurity in

commercial supplies and a better sense of whether the conjecture about that impurity as a cause of sensitization and not the named ingredient has any merit."

I didn't see that. So I don't know what we say in the -- I'm looking in the discussion to see if they mention anything about impurities.

MR. JOHNSON: No, we don't.

DR. SHANK: I don't see it.

DR. BERGFELD: Because we don't have a discussion.

DR. SHANK: So I guess we can discuss that tomorrow.

DR. MARKS: Yes. Okay.

DR. BERGFELD: So are you going to go along with the insufficient?

DR. MARKS: Oh, I think so.

DR. SHANK: Yes.

MR. JOHNSON: Actually, I just want to make sure that I have all the data needs. You said the phototoxicity data?

DR. SHANK: Yes. He said we need phototoxicity data, and we need -- I'll just summarize this. I guess we need a discussion on is 3-Capryloyl, which is an impurity, the real cause of sensitization and not the ingredient in itself.

MR. JOHNSON: Okay.

DR. MARKS: I think that's, perhaps, speculation. And once we have the NESIL, it really doesn't matter.

DR. SHANK: Okay. That's good.

DR. MARKS: That's how I would approach it.

MR. JOHNSON: So just one item, the phototoxicity?

DR. SHANK: Yes, the phototox.

MR. JOHNSON: And that is on -- okay.

DR. MARKS: So, Tom and Ron, you like the idea of an insufficient data announcement tomorrow, rather than moving on to a conclusion with safe when formulated to be non-irritating and non-sensitizing?

DR. SLAGA: We'll see how one more time -- we can give it a try.

DR. MARKS: Yeah. Okay. We'll see what the motion is tomorrow. You're giving us a window into what the motion probably is going to be, Wilbur. Thank you.

MR. JOHNSON: You're welcome.

DR. MARKS: I still may present it as the alternative, and then just let Don react to that and see what he says.

DR. BERGFELD: Well, he'll be proposing the motion, so you were not going to second it? Is that correct?

DR. MARKS: I probably will second it and then, when we do the discussion, just mention it. We'll see. Obviously, I think, to give a little bit more time and thought, the insufficient data announcement is the safer way to go. If the NESIL answers and makes the conclusion crisper, I like that. Okay. Any other comments about these ingredients?

DR. SHANK: No, not here.

DR. BELSITO: Okay, so, this came about because we discovered that this was not a salicylic acid ester but was rather a ketone. So it was split out of the salicylic acid group that we had looked at previously. And, there was quite a bit of data here, but not all of it sufficient. So, it is insufficient for impurities, and we need to run a QRA off the HRIPTs because there is sensitizing capacity. There's also an irritating capacity. So, that we can go with by saying formulated to be nonirritating, but we need some sense of the QRA on this based off of the HRIPTs that we have. And we need more information on impurities.

DR. BERGFELD: And that is a conclusion, or that is an insufficient --

DR. BELSITO: Insufficient announcement.

DR. BERGFELD: -- right, a motion.

DR. BELSITO: It's the first time we're looking at it.

DR. BERGFELD: Okay.

DR. MARKS: We second that. And then, Ron Hill brought up the issue of phototoxicity data. Do we need that or not? And if we're unsure, we could just list that as one of the insufficiencies and then address it at the next time we see this ingredient.

DR. BERGFELD: Is that agreeable?

DR. BELSITO: No, I mean, I'm not sure why he's bringing that up.

DR. MARKS: He felt the structure, I'm sure it potentially could be a --

DR. LIEBLER: Yeah. It looks like an alkyl phenome structure. But the thing is it's got the carboxyl and phenyl substituents on it. I think both of those would mitigate against photo activation. I mean, at first glance with one eye close it looks like acetophenone, I understand what he's reacting to. But I don't think it's necessary.

DR. MARKS: Okay. Fine

DR. BELSITO: I mean, we could, rather than ask for phototoxic, if there's any concern, why not ask for a UV spectrum? If it doesn't absorb then there's no issue.

DR. LIEBLER: Oh, it'll absorb, for sure.

DR. BELSITO: Okay.

DR. BERGFELD: So are we adding the phototox request, or not?

DR. BELSITO: Dan?

DR. MARKS: I'd suggest we could add it and then come back to it again. And if you still feel that it's unlikely a phototoxic reaction would occur, based on the chemical structure, then we can just delete that insufficiency the next time.

DR. LIEBLER: Sure, I'm okay with that. I think we could add that, and we'll see what they come back with.

DR. MARKS: Okay.

DR. BERGFELD: Ron Shank?

DR. SHANK: You want me to read Dr. Hill's comment? Not necessary.

DR. MARKS: I don't think so, since that was the main -- he also mentioned about impurities, it possibly being a sensitizer. But that really isn't relevant to the IDA; we're already asking about that as you said through the QRA. So, I think we can add the phototox and we'll address it again at the -- see if we get a --

DR. BELSITO: We're also asking for impurities.

DR. MARKS: Right.

DR. BERGFELD: So, may we read the list of what is needed?

DR. SHANK: May I make a comment?

DR. MARKS: Okay.

DR. SHANK: Why do you need impurities? We have genotoxicity data, it's negative. We have DART data, negative, human sensitization, negative. Why do you need to know what the impurities are? Other than being complete?

DR. BELSITO: I'll let Dan answer that. We have negative data in humans at certain concentrations. However, it is a sensitizer because it was positive in a guinea pig maximization test. So it has the capability to sensitize, so we need to look at what that capability is.

DR. SHANK: Just say, when formulated to be non-sensitizing. Do that all the time. Why do you have to have impurities?

DR. LIEBLER: So we always ask for impurities.

DR. SHANK: Okay, checking the box.

DR. LIEBLER: Yeah, it's more checking the box then anything. And I would be satisfied with something a little bit better than what it is. Currently, it's reported that the structural isomer, blah, blah, blah is a highly plausible contaminant. In other words, I'll bet you a beer that this might be an impurity. And you just tell us is this 99 percent, and if you have other information on impurities, put it in there, a sentence or so, we're good.

DR. SHANK: Thank you.

DR. BELSITO: I just want to hold on here one second.

DR. BERGFELD: So we have a motion -- I'm just going to talk over you a little bit while you look -- motion to go as an IDA, Insufficient Data Announcement.

DR. BELSITO: Right.

DR. BERGFELD: We have, we believe, I think Wilbur's written them down, the needs that have been requested. Would you repeat these?

MR. JOHNSON: Yes, the impurities data, QRA based upon the positive for guinea pig sensitization test data, and phototoxicity data.

DR. BERGFELD: Okay.

DR. MARKS: Yes.

DR. BERGFELD: And we have the proposal motion by Don. Are you --?

DR. MARKS: Oh, I seconded that.

DR. BERGFELD: -- second that?

DR. MARKS: I think I heard Don say a little bit differently the QRA based on the human sensitization, not on the guinea pig.

DR. BELSITO: I'm just looking here; it may not be needed. Two percent non-sensitizing HRIPT and 102, and 106 at .5, and the max leave-on concentration is .5. Is that correct?

DR. SNYDER: .5 in leave-on.

DR. BELSITO: .5 in leave-on. So then, yes. Just safe as used? Because its use is below what the HRIPT and the human HRIPT was.

DR. BERGFELD: So are we retracting the motion?

DR. BELSITO: We're retracting the motion for a QRA.

DR. BERGFELD: Are we retracting anything else in this list?

DR. BELSITO: No impurities and phototox.

DR. BERGFELD: Okay. Ron Shank, you want to make a comment on that? I see you smiling.

DR. SHANK: No more comments from me.

DR. BERGFELD: All right. So there's an agreement about an insufficient data announcement. We have the needs and they've been recounted several times, and one being removed. I call the question of going forward, all those in favor? Thank you. Moving on --

DR. MARKS: In anticipation, once we -- on the next time we review this, issue a tentative amended report, are we going to still put in there, since the guinea pig max was positive, meaning sensitization, that we're going to have a non-sensitizing part of the conclusion?

DR. BELSITO: No, I mean, I think what we need to do in the discussion is say that, you know, the guinea pig maximization test indicated the potential for sensitization; however, two well-conducted HRIPTs, one at .5 and one at two percent and humans were negative. And, therefore, as currently used, max .5 in a leave-on, it's safe as used.

DR. MARKS: And I might also add, Don, in there that our clinical experience supports that conclusion in the discussion. Because, if I recall correctly, in the past you've said the HRIPT is not adequate enough when you have a sensitization alert, depending on where it's used and how it's used. Ala the MCI/MI or MI in wipes was a significant sensitizer. So, I think I'd put in the discussion at least that we're reassured with the HRIPT results and the clinical, which would indicate that it's not a significant sensitizer.

DR. BELSITO: Particularly since one of the HRIPT was at four times what is the reported max leave-on.

DR. MARKS: Yeah, I think that all could be captured in the discussion. Okay?

DR. BERGFELD: Any other comments? All right, moving on to the next ingredient, which is the third ingredient in this group, the citrates.

Capryloyl Salicylic Acid Data Profile* –September 16-17, 2019 Panel – Wilbur Johnson

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Capryloyl Salicylic Acid	**X**	**X**	X	X	X		X	X		X	X		X	X	X	X				X	X		X	X			X	X	X

* “X” indicates that data were available in a category for the ingredient

[Capryloyl Salicylic Acid – 7/31/2019]

Ingredient Names (for same ingredient)	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS*	NICNAS	NTIS	NTP	WHO	FAO	ECET -OC	Web
Capryloyl Salicylic Acid	78418-01-6	Yes	76/0	6/5	1/1	No	No	No	No	No	Not Searchable	Yes	No	No	No	No	No	
5-Octanoylsalicylic acid	78418-01-6		32/0	0	1/0	No	No	No	No	No	Ditto	No	No	No	No	No	No	
2-Hydroxy-5-octanoyl benzoic acid	78418-01-6		7/0	4/4	1/1	No	No	No	No	No	Ditto	Yes	No	No	No	No	No	
2-Hydroxy-5-octanoylbenzoic acid	78418-01-6		21/0	12/9	10/10	No	No	No	No	No	Ditto	No	No	No	No	No	No	
78418-01-6 (alone)	0		202/1	0	0/0	No	No	Yes	REACH dossier	No	Ditto	No	No	No	No	No	No	

*Database not searchable due to effects of Government Shutdown

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/

RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers
Absorption
Acute
Allergy
Allergic
Allergenic
Cancer
Carcinogen
Chronic
Development
Developmental
Excretion
Genotoxic
Irritation
Metabolism
Mutagen
Mutagenic
Penetration
Percutaneous
Pharmacokinetic
Repeated dose
Reproduction
Reproductive
Sensitization
Skin
Subchronic
Teratogen
Teratogenic
Toxic
Toxicity
Toxicokinetic
Toxicology
Tumor

Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics

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The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; 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 Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of Capryloyl Salicylic Acid in cosmetic products; this ingredient is reported to function as a skin conditioning agent. The Panel reviewed relevant data relating to the safety of this ingredient in cosmetic formulations, and concluded that …[to be determined].

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of Salicylic Acid and 16 salicylates in 2003.[1] That safety assessment included Capryloyl Salicylic Acid, which was included in the grouping because at the time, it was mischaracterized and defined as an ester. However, it is now known that this ingredient is a ketone, and it does not belong in that family of ingredients; therefore, a separate report has been prepared. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Capryloyl Salicylic Acid is reported to function as a skin conditioning agent.[2]

The published data in this document were identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data may be provided by the cosmetics industry, as well as by other interested parties. Much of the data included in this safety assessment was found at the European Chemicals Agency (ECHA) and National Industrial Chemicals Notification and Assessment Scheme (NICNAS) websites.[3,4] Please note that these websites provide summaries of information from other studies, and it is those summary data that are reported in this safety assessment when ECHA or NICNAS is cited.

CHEMISTRY

Definition and General Characterization

Capryloyl Salicylic Acid (CAS No. 78418-01-6) was previously, erroneously, defined as the ester of salicylic acid and caprylic acid. However, it has become apparent that Capryloyl Salicylic Acid is instead the 5-capryl ketone of salicylic acid. As such, this chemical is structurally distinct from the salicylate carboxyl esters. It is now defined as the organic compound that conforms to Figure 1.[2]

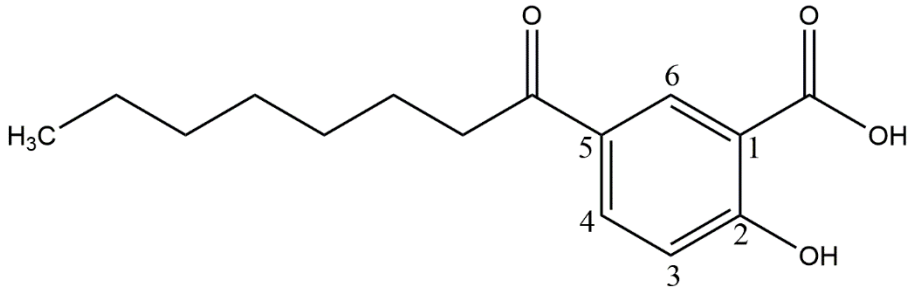

Figure 1. Capryloyl Salicylic Acid

Chemical and Physical Properties

Capryloyl Salicylic Acid has a molecular weight of 264 Da and has an 8-carbon acyl fatty chain linked to the fifth carbon of the benzene ring.[5] This white powder is water soluble (29.7 mg/mL) and acidic (estimated pKa of 2.68). According to information submitted for the ECHA dossier, the particle size distribution of this ingredient as a raw material includes 13.23 – 26.71% of particles < 100 μm;[3] however, the bearing of these raw material particles sizes on the particle sizes of final consumer product formulations is not clear. Further chemical and physical properties of Capryloyl Salicylic Acid are presented in Table 1.[3,6]

Method of Manufacture

The synthetic method of manufacture for Capryloyl Salicylic Acid is based on Friedel-Crafts acylation of methyl salicylate by capryloyl chloride and aluminum trichloride to yield the methyl ester of Capryloyl Salicylic Acid.[7] This ester is hydrolyzed with sodium hydroxide, after which acidification yields Capryloyl Salicylic Acid.

Impurities

It has been reported that the structural isomer, 3-capryloyl salicylic acid, is a highly plausible contaminant of Capryloyl Salicylic Acid.[7]

USE

Cosmetic

The safety of this cosmetic ingredient is evaluated based, in part, on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics.[8] Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[9]

According to 2019 VCRP data, Capryloyl Salicylic Acid is reported to be used in 104 cosmetic products (93 leave-on and 11 rinse-off).[8] The results of a concentration of use survey conducted in 2018 indicate that Capryloyl Salicylic Acid is used at concentrations up to 0.5% (in moisturizing products, not spray), which is the highest reported maximum use concentration for leave-on formulations.[9] In rinse-off products, Capryloyl Salicylic Acid is reported to be used at concentrations up to 0.4% (in paste masks and mud packs), which is the highest reported maximum use concentration for rinse-off formulations. Further use frequency and concentration of use data are presented in Table 2.

Cosmetic products containing Capryloyl Salicylic Acid may be applied to the skin at concentrations up to 0.5% (moisturizing products, not spray) and may come in contact with the eyes during use of eye lotions and other eye makeup preparations (use concentrations were not reported by industry). Capryloyl Salicylic Acid also could be incidentally ingested during product use (e.g., use concentrations up to 0.1% in lipsticks). Products containing Capryloyl Salicylic Acid may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Capryloyl Salicylic Acid is reported to be used in deodorant sprays (aerosolized) at concentrations up to 0.3%. 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.[10,11,12,13] 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.[10,11] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[11] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Capryloyl Salicylic Acid is being used in face powders at concentrations up to 0.3%. 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.[14,15,16]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

The penetration of Capryloyl Salicylic Acid through human skin was assessed using a Franz diffusion chamber and skin samples.[5] The amount of Capryloyl Salicylic Acid that penetrated deeper than the stratum corneum after a 16-h contact time was significantly lower than its parent acid, salicylic acid, in the same vehicle. Thus, only approximately 6% of Capryloyl Salicylic Acid was found to penetrate deeper than the stratum corneum, after 16 h, versus 58% for salicylic acid.

Human

The skin penetration of Capryloyl Salicylic Acid was also assessed using a standard stripped skin method.[5] Capryloyl Salicylic Acid was applied to the skin (number of subjects involved not stated), followed by rinsing with water/alcohol 30 min later. Strips of stratum corneum were then harvested, using adhesive tape, and analyzed for test material content. An estimation of the level of penetration through the skin over a 4-day period was determined using the

stored concentration method. Based on this method, 17.1% of the applied test material was found in the stratum corneum, versus 9.7% of salicylic acid applied.

Absorption, Distribution, Metabolism, and Excretion

Data on the absorption, distribution, metabolism, and excretion of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Capryloyl Salicylic Acid was studied using Sprague-Dawley rats (5 males, 5 females).[3] The study was performed according to Organization for Economic Co-operation and Development (OECD) Test Guideline (TG) 402. A semi-occlusive patch (7 cm x 4 cm) containing the test substance (in peanut oil) was applied for 24 h to an area defined as 10% of the total body area. This amounted to a single dose exposure of 2000 mg/kg. Dosing was followed by a 14-day observation period, after which the animals were killed. Necropsy was performed, but tissues were not retained. None of the animals died during the observation period, but the following signs of toxicity were observed: hunched posture, lethargy, and piloerection during the first day. With the exception of 1 male rat, body weight gain was not affected by treatment. The following adverse dermal reactions were observed: edema and blanching and hard, light brown colored scabs at the application site. These findings were accompanied by loss of the upper layers of skin and fur, resulting in purple/pink areas. The distribution of toxicity signs/adverse dermal reactions in the dosed group was not reported. The LD_{50} was > 2000 mg/kg.

Oral

The acute oral toxicity of Capryloyl Salicylic Acid (in peanut oil) was evaluated using groups of 10 Sprague-Dawley rats (5 males, 5 females/group).[3] The four dose groups received single oral doses (by gavage) of 2530, 3000, 3557, and 4217 mg/kg, respectively. The study was performed according to OECD TG 401. A control group was not included in the study. Dosing was followed by a 14-day observation period. All animals were subjected to gross necropsy. The following major signs of toxicity were observed in all dose groups: hunched posture, piloerection, lethargy, ptosis, decreased or gasping respiration, red/brown staining around the snout or mouth, and ataxia and/or increased. Incidences of reduced body weight gain or body weight loss also occurred in all dose groups. Distended abdomen and/or emaciation were observed in animals of the 3 higher dose groups. Pallor of the extremities, with an isolated incidence of tiptoe gait, was observed in animals of the 3557 mg/kg dose group. Mortalities in all dose groups were reported as follows: 2530 mg/kg (1 female); 3000 mg/kg (4 males and 2 females); 3557 mg/kg (3 males, 3 females), and 4217 mg/kg (4 males, 4 females). The following abnormalities were observed at necropsy of animals that died during the study: hemorrhagic or abnormally red lungs; dark liver or patchy pallor of the liver; pale spleen; pale or dark kidneys; hemorrhage or sloughing of the glandular gastric epithelium; and hemorrhage of the small and/or large intestines. Abnormalities observed at necropsy of animals (2530 g/kg group) that were killed at the end of the study were described as occasional white foci (~1 mm x 1 mm covering 75% of the non-glandular gastric epithelium). At necropsy, there were no abnormalities in animals that received a dose of 3000 mg/kg or higher and were killed at the end of the study. The combined oral LD_{50} (males + females) for the test material was 3354 mg/kg (95% confidence limit between 2834 and 3970 mg/kg).

Results relating to acute oral toxicity are included in a micronucleus test on Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle).[4] The micronucleus test (described later in this report), performed in accordance with OECD TG 474, used groups of 10 (5 males, 5 females per group) Swiss CD-1 mice. A single dose of the test substance (500, 1000, and 2000 mg/kg) was administered by gavage to 3 groups, respectively. Two female mice and 1 male mouse dosed with 2000 mg/kg were found dead 24 h after dosing. Piloerection was observed in all animals on the same day of dosing with 1000 mg/kg. Piloerection and swollen abdomen were observed in the 2000 mg/kg dose group.

Results relating to acute oral toxicity are also included in an unscheduled DNA synthesis test on Capryloyl Salicylic Acid (in 0.5% in carboxymethylcellulose aqueous vehicle).[4] The assay was performed in accordance with OECD TG 486 using groups of 4 Sprague-Dawley rats. In 2 tests, single doses of 500, 1000, and 2000 mg/kg were administered by gavage. The animals were killed at 14 h in one test and at 2 h in the other test. No mortalities or clinical signs were observed. (Results relating to genotoxicity are included in that section of this report.)

Short-Term Toxicity Studies

Dermal

A short-term dermal toxicity study (10-day study) on Capryloyl Salicylic Acid (in hexaethylene glycol (PEG-6)) was performed using groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain.[3] The test substance was applied for 6 h directly to the back (not less than 10% of body area; constant volume of 2 mL/kg) once daily at concentrations of 2% and 5%. A third group was treated with vehicle only. The test protocol was similar to OECD TG 410. None of the animals died during the study. The animals were killed at the end of the 10-day dosing period and subjected to gross necropsy. Tissues were examined microscopically. There were no treatment-related changes in food consumption or body weight gain. The authors noted that occasional transient weight losses were observed which, because of the small group sizes, skewed the means. Other than the scabbing that was observed at necropsy, there were no other necropsy findings. The no-observed-effect-levels (NOEL) for local and systemic effects of Capryloyl Salicylic Acid were 2% and > 5%, respectively. Additional results from this study are included in the Skin Irritation section of this report.

The skin sensitization potential of Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) was evaluated in the guinea pig maximization test, according to OECD TG 406.[4] Twenty Dunkin-Hartley guinea pigs (10 males, 10 females) were tested with this ingredient in this study. During topical induction, Capryloyl Salicylic Acid was applied at a concentration of 1%. One animal was found dead on day 18, but microscopic examination revealed no apparent abnormalities. None of the other animals had clinical signs; body weight gains were comparable to the control animals. Results relating to skin sensitization potential are included in that section of this report.

Oral

A short-term oral toxicity study on Capryloyl Salicylic Acid (in PEG-6) was performed using groups of 10 or 20 rats of the CRL:CD(SD)BR strain.[3] The control group and highest dose group (initially, 300 mg/kg/day) each consisted of 20 rats (10 males, 10 females per group). Each of the remaining dose groups (10, 30, and 100 mg/kg/day) consisted of 10 rats (5 males, 5 females per group). The animals were dosed orally (by gavage) daily for 28 days in accordance with OECD TG 407. Two recovery groups (5 males, 5 females per group; for control and highest dose groups) were maintained un-dosed for an additional 14 days after the last day of dosing (day 28). The dose level in the highest dose group was reduced from 300 to 200 mg/kg/day on day 13 due to adverse clinical signs, including death. The animals were subjected to gross necropsy and microscopic examination of tissues at the end of the study. Five rats from the highest dose group died during the study, and the following clinical signs were observed: rough coat, piloerection, post-dose salivation. A slight reduction in body weight gain (13 to 14%) was also noted in males of the highest dose group during treatment and non-treatment periods, and in females of the 100 mg/kg dose group during treatment only. Hematology and blood chemistry evaluations did not reveal any adverse effects. At necropsy, a dose-related increase in the incidence of stomach abnormalities was observed (at the end of both the treatment and the treatment-free period) for animals dosed with 100 mg/kg/day and 300/200 mg/kg/day. Microscopic findings included hyperplasia of the non-glandular stomach in animals of the 300/200 mg/kg/day group. This finding was accompanied by chronic inflammation and ulceration. Hyperplasia was also observed in 1 male in the 100 mg/kg/day dose group. Similar, but less severe, hyperplastic lesions were also observed in recovery animals that were previously dosed with 300/200 mg/kg/day. Hyperplasia of the non-glandular mucosa of the stomach was less severe at the end of the treatment-free period, which indicates that some recovery had taken place. Additionally, reversibility was observed and the effects were limited to the non-glandular stomach, and, thus, were considered to be of doubtful relevance to humans. The NOEL for local effects was 30 mg/kg/day, and the NOEL for systemic effects was > 100 mg/kg/day.

Subchronic Toxicity Studies

Data on the subchronic toxicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

Chronic Toxicity Studies

Data on the chronic toxicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Animal

Dermal

The developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 24 pregnant female Sprague-Dawley rats.[3] The 2 test groups received doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. The vehicle control group was dosed with PEG-6. The test substance and vehicle control were each applied for 6 h directly to skin on the back (not less than 10% of the body area). On gestation day 20, all females were killed and subjected to necropsy. Numbers of corpora lutea and live and dead implantations were recorded. Live fetuses were examined for external and visceral abnormalities. One-half of the fetuses were subsequently examined for skeletal abnormalities. No premature deaths or treatment-related clinical signs were recorded during the study. There was no treatment-related effect on mean maternal food consumption and body weight. However, when compared to the control group, a statistically significant reduction in body weight gain values was reported for the 40 mg/kg/day dose group (gestation days 9 - 12) and for the 100 mg/kg/day dose group (gestation days 6 - 15). There were no treatment-related effects on pregnancy parameters, mean fetal weight, and incidences of major external, visceral, or skeletal abnormalities.

When compared to the background range, a higher (but not statistically significant) increase in the incidence of minor skeletal abnormalities and variants (including incomplete ossification of the sacral neural arch) was observed in the vehicle control group and both dose groups. The historical control range was from 0% to 9%, compared to a value of 18.3% for the incidence of sacral neural arch incomplete ossification in the vehicle control group. Therefore, the authors noted the likelihood that the incidence of the skeletal minor abnormalities observed in both dose groups was also overestimated. Furthermore, they noted that these statistically non-significant skeletal findings in both dose groups were likely related to the transient, but statistically significant, decrease in body weight gain observed in dams (gestation days 9 - 12). This decrease was attributed to the moderate or severe skin lesions that led to pain and stress in the animals. Therefore, it was determined that the increase in the incidence of skeletal variations reported for fetuses from both groups were likely secondary to maternal toxicity (induced by local effects leading to pain and stress) and not indicative of a teratogenic effect. Results relating to maternal skin irritation potential are included in the Skin Irritation section of this report.[3] A no-observed-adverse-effect-level (NOAEL) was not reported in this study summary. However, the following conclusion is reported in a summary of this study from a different source, "The NOAEL for developmental toxicity was established as 40 mg/kg/day, based on an increase in the incidence of fetuses with incomplete ossification of the sacral neural arch at 100 mg/kg/day."[4] The NOAEL was not established for maternal toxicity, as treatment-related effects (local reaction at the site of administration and reductions in body weight gain) were observed at both doses tested.

Oral

The reproductive and developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 20 (10 males, 10 females per group) Wistar Hannover rats.[3] The animals were dosed orally (by gavage) with the test substance once daily in accordance with OECD TG 421. The 3 dose groups received 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day, respectively (dose volume of 4 mL/kg/day). Male rats were dosed 2 weeks prior to mating, during the mating period, and up to 5 weeks post-mating (50 days total). Female rats were dosed 2 weeks prior to mating, during the mating period (up to 14 days), during gestation, and at least 4 additional days during the lactation period (40 to 49 days total). The vehicle control group was dosed with PEG-6. At the end of the dosing period, all parental animals were killed and subjected to gross necropsy. Histopathological examination of tissues was performed. There were no mortalities or clinical signs that were attributed to treatment with the test substance, and there were no effects on body weight and food consumption. The following parameters in treated animals were similar to those of the vehicle control group: reproductive performance of males and females, mating, fertility, gestation, and live birth indices. There were no treatment-related effects on weights of testes, epididymides, ovaries, uterus, and cervix. Furthermore, there were no treatment-related findings at necropsy or microscopic examination. There also were no effects on the clinical condition of pups, body weight, or sex ratio. No macroscopic findings were noted in pups that were killed on day 4 post-partum. The NOEL of Capryloyl Salicylic Acid was considered to be 100 mg/kg/day for the following: parental toxicity, embryo-fetal developmental toxicity, and pup development until day 4 post-partum.

GENOTOXICITY STUDIES

The following genotoxicity studies on Capryloyl Salicylic Acid that are summarized below are described in Table 3.

In Vitro

The genotoxicity of Capryloyl Salicylic Acid (in ethanol) was evaluated in the Ames test using the following bacterial strains, with and without metabolic activation: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvr A.[3] Doses up to 1000 µg/plate were tested, and the test material was classified as non-genotoxic. The mammalian chromosome aberration test involving Chinese hamster ovary cells (with and without metabolic activation) was used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in ethanol) at concentrations of 50 µg/mL and 80 µg/mL.[4] The test material was classified as clastogenic with, but not without, metabolic activation.

In Vivo

The genotoxicity of Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle) was evaluated in the micronucleus test using groups of 10 (5 males, 5 females per group) mice of the CD-1 strain.[3] A single dose of the test substance (250, 500, and 1000 mg/kg) was administered by gavage to the 3 groups, respectively. The test material was classified as non-clastogenic. In a second micronucleus test, Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) was administered to groups of 10 (5 males, 5 females per group) Swiss CD-1 mice.[4] A single dose of the test material (500, 1000, and 2000 mg/kg) was administered by gavage to the 3 groups, respectively. A slight increase in the polychromatic erythrocytes (PCEs)/normochromatic erythrocytes (NCEs) ratio was observed in males of the 2000 mg/kg dose group, only at the 24-h sampling time. This finding was indicative of an inhibitory effect on erythropoietic cell division. Results indicated that the test material was non-clastogenic in this assay. (Results relating to the acute oral toxicity of this test material are included in that section of this report.) The unscheduled DNA synthesis test was also used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose), using groups of 4 Sprague-Dawley rats.[4] In 2 tests, single doses of 500, 1000, and 2000 mg/kg were administered by gavage, and the test material was classified as non-clastogenic in both. (Results relating to acute oral toxicity are included in that section of this report.)

CARCINOGENICITY STUDIES

Data on the carcinogenicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The skin irritation and sensitization studies summarized below are presented in detail in Table 4.

The skin irritation potential of Capryloyl Salicylic Acid was evaluated in a 4-h occlusive patch test using 3 male New Zealand White rabbits.[3] The animals were patch tested with 0.5 g (applied to 62.5 mm^2 area) of the test material, and results were negative. In a study involving groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain, Capryloyl Salicylic Acid (in PEG-6) was applied to the back (constant volume of 2 mL/kg) once daily for 10 days. The test material was applied at concentrations of 2% and 5%; only the 5% concentration caused very slight erythema (in 2 to 5 rats) and edema (3 or 4 rats). Minimal/moderate scabbing at the application site was also observed. (Additional results from this study are included in the Short-Term Dermal Toxicity section of this report.) Skin irritation data are reported in a developmental toxicity study (described previously) on Capryloyl Salicylic Acid (in PEG-6) involving 2 groups of 24 pregnant female Sprague-Dawley rats.[3] The test material was applied to skin of the back (2 groups) at doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. Erythema and eschar formation were observed in both groups (number of animals not stated), the severity of which was dose-related. Slight edema was also reported, and scabbing and/or reddening at test sites was observed at necropsy.

Reactions described as cutaneous signs of slight intensity were observed in 5 of 49 subjects after application of a face product containing 0.3% Capryloyl Salicylic Acid to the face and eye contour twice daily for 4 weeks.[4]

The skin sensitization potential of Capryloyl Salicylic Acid (in arachis oil) was evaluated in the guinea pig maximization test, using 20 female Dunkin-Hartley guinea pigs.[3] Induction involved intradermal injection and topical application of 1% and 0.5% concentrations, respectively. This was followed by challenge with 0.5% (occlusive patch). The test material was classified as a skin sensitizer. In another maximization test, 20 guinea pigs were tested with Capryloyl Salicylic Acid (in ethanol).[4] Induction involved intradermal injection and topical application of 0.5% and 10% concentrations, respectively. There were no signs of skin irritation during induction at concentrations of 0.5% (injected intradermally) and 10% (topical application). The animals were challenged with 2%. Sensitization reactions were observed (at 24 h and 48 h) at the application sites of 5 guinea pigs. However, these findings were classified as limited evidence of skin sensitization. The skin sensitization potential of Capryloyl Salicylic Acid (in PEG-300) was also evaluated in the maximization test, using 20 guinea pigs.[4] The induction phase involved concentrations of 25%, 15%, and 10%. When a concentration of 25% was applied, several test animals (number not stated) had erythema scores of 2 or more at the

application site after the first induction application. The concentration was decreased during induction because of skin irritation, and induction was followed by topical challenge with 5%. At 24 h, but not 48 h, sensitization reactions were observed at the application sites of 2 animals. These findings were classified as limited evidence of skin sensitization. Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) was evaluated for sensitization potential in the guinea pig maximization test, using 20 Dunkin-Hartley guinea pigs.[4] A test concentration of 1% was used for topical induction and challenge. Skin reactions were not observed in any of the test animals during induction or the challenge phase, and the test material was classified as a non-sensitizer. Results relating to short-term dermal toxicity reported in this maximization test are included in that section of this report.

In 2 human repeated insult patch tests (HRIPTs), involving 106 subjects in one study and 105 subjects in the other, a face serum product containing 0.5% Capryloyl Salicylic Acid was classified as a non-sensitizer.[4] In the study involving 106 subjects, slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A cream product and a fluid cream product (each containing 0.5% Capryloyl Salicylic Acid) were also classified as non-sensitizers in HRIPTs involving 104 subjects and 106 subjects, respectively. A cosmetic product containing 2% Capryloyl Salicylic Acid was classified as a non-sensitizer in an HRIPT involving 102 subjects.[4] Slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A face powder containing 2% Capryloyl Salicylic Acid and a deodorant aerosol product containing 2% Capryloyl Salicylic Acid were also classified as non-sensitizers in HRIPTs involving 105 subjects and 103 subjects, respectively.[4]

OCULAR IRRITATION STUDIES

Animal

The ocular irritation potential of Capryloyl Salicylic Acid was evaluated using 3 New Zealand White rabbits, according to OECD TG 405.[3] The test substance (~ 65 mg) was instilled into the eye, and exposure was not followed by ocular rinsing. Reactions were scored at 24 h, 48 h, and 72 h after instillation, and the animals were observed for a total of 14 days after exposure. Diffuse corneal opacity, iridial inflammation, and moderate or severe conjunctivitis were observed in all treated eyes at 1 h post-instillation and in 2 treated eyes at 24 h, 48 h, and 72 h post-instillation. In the eye of 1 treated animal, corneal opacity increased and areas of opalescent corneal opacity with iridial inflammation and moderate to severe conjunctival irritation were observed at 48 h and 72 h post-instillation. Adverse effects observed on the nictitating and/or conjunctival membranes in the eye of this animal were described as pale appearance, small green-colored or white areas, and areas of hemorrhage. In another rabbit, diffuse corneal opacity, iridial inflammation, and minimal conjunctival irritation persisted in the treated eye on day 7; these effects were resolved by day 14. Circumcorneal vascularization and convoluted eyelids were also noted in this animal, and the nictitating membrane was also pale in appearance. In the third rabbit, corneal opacity increased and opalescent corneal opacity with pannus formation (indicative of irreversible ocular damage) had developed on day 14. It was not possible to assess iridial inflammation at this time, and minimal conjunctival irritation with convoluted eyelids were also observed. Capryloyl Salicylic Acid was classified as a severe irritant to the rabbit eye.

Human

A face product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 49 subjects twice a day for 4 weeks.[4] The group included subjects with sensitive skin, sensitive eyes, non-sensitive eyes, and contact lenses wearers. According to the authors, “observations were recorded before application and at least 10 min after the first application and the last application respectively.” Microscopic examinations of ocular and periocular structures revealed no appearance of ocular physical signs or palpebral signs. Colorimetric examinations of the cornea and the conjunctiva revealed a maximal corneal index of 0.50% and a maximal conjunctival index of 0%, indicating an absence of toxicity to the conjunctiva and a very slight toxicity to the cornea. Clinical examinations revealed an ocular irritation rate of 0.03% and an ocular comfort rate of 99.83%. Additionally, the product did not induce any pathology that was specific to contact lenses wearers.

An eye contour product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 50 subjects twice a day for 4 weeks.[4] The group included subjects with sensitive eyes, non-sensitive eyes, and contact lenses wearers. Observations were recorded before application and at least 10 min after the first application and the last application, respectively. The product induced moderate ocular burning in 1 subject with sensitive eyes, and slight ocular stinging in 1 contact lenses wearer. Biomicroscopic examinations of ocular and periocular structures revealed 2 bilateral occurrences of bulbar conjunctival redness in 2 subjects. Colorimetric examinations of the cornea and the conjunctiva revealed a maximal corneal index of 0% and a maximal conjunctival index of 0%, indicating an absence of toxicity to the conjunctiva and very slight toxicity to the cornea. Clinical examinations revealed an ocular irritation rate of 0.04% and an ocular comfort rate of 99.88%. Additionally, the product did not induce any pathology that was specific to contact lenses wearers.

CLINICAL STUDIES

Case Reports

A female patient who used day and night creams containing Capryloyl Salicylic Acid presented with dermatitis of the face, which was first observed 3 months earlier.[17] Positive patch test reactions (+) to both products and to Capryloyl Salicylic Acid (1% in alcohol) were reported. Another female patient who used the same night cream containing Capryloyl Salicylic Acid also presented with facial dermatitis and had a positive patch test reaction to this ingredient (1% in alcohol).

A female patient presented with a pruritic erythematous rash that arose on her face 10 days after application of a cream containing Capryloyl Salicylic Acid (concentration not stated). A positive allergic reaction (++) to 1% Capryloyl Salicylic Acid in alcohol was observed in the patient (at 48 h and 96 h), but not in 15 healthy control subjects.

In a letter to the editor on the preceding 2 case reports, the author stated that Capryloyl Salicylic Acid is unlikely to be significantly allergenic, and is therefore unlikely to be the cause of the contact allergy reported.[7] However, the structural isomer, 3-capryloyl salicylic acid, is a highly plausible contaminant of Capryloyl Salicylic Acid and is likely to be sufficiently allergenic to account for the observed contact allergy.

Other Clinical Reports

In a split-face study, 44 female volunteers with mild to moderate facial hyperpigmentation and fine lines/wrinkles were randomized, and a Capryloyl Salicylic Acid containing peel was applied to one side of the face.[18] Increasing peel concentrations were applied (5 - 10% Capryloyl Salicylic Acid) based on the tolerance level of the subjects and clinical observations of an expert dermatologist for 12 weeks at biweekly intervals. Results indicated that there were no significant changes in erythema for Capryloyl Salicylic Acid from baseline values when compared with pre-peel to pre-peel and post-peel to post-peel at different weeks.

SUMMARY

Capryloyl Salicylic Acid was previously, erroneously, defined as the ester of salicylic acid and caprylic acid. However, is has become apparent that Capryloyl Salicylic Acid is, instead, the 5-capryl ketone of salicylic acid. Capryloyl Salicylic Acid can be manufactured via Friedel-Crafts acylation of methyl salicylate with capryloyl chloride and aluminum trichloride, to yield the methyl ester of Capryloyl Salicylic Acid, which is then hydrolyzed with sodium hydroxide, after which acidification yields this ketone, Capryloyl Salicylic Acid.

Capryloyl Salicylic Acid is reported to be used in 104 cosmetic products (93 leave-on and 11 rinse-off). The results of a concentration of use survey conducted in 2018 indicate that Capryloyl Salicylic Acid is used at concentrations up to 0.5% (in moisturizing products, not spray), which is the highest reported maximum use concentration for leave-on formulations. In rinse-off products, Capryloyl Salicylic Acid is used at concentrations up to 0.4% (in paste masks and mud packs), which is the highest reported maximum use concentration for rinse-off formulations.

In vitro skin penetration data (human skin samples) indicate that, after 16 h of contact, ~ 6% of the applied Capryloyl Salicylic Acid was found to "penetrate deeper than the stratum corneum." Using a standard tape stripping method for determining skin penetration (number of subjects not stated), it was determined that 17.1% of Capryloyl Salicylic Acid applied to the skin of human subjects was found in the stratum corneum over a 4-day period.

The acute dermal toxicity of Capryloyl Salicylic Acid was studied using Sprague-Dawley rats (5 males, 5 females). An LD_{50} of > 2000 mg/kg was reported. The following adverse dermal reactions were observed after a single oral dose of 2000 mg/kg: edema and blanching and hard, light brown colored scabs at the application site.

The acute oral toxicity of Capryloyl Salicylic Acid (in peanut oil) was evaluated using groups of 10 Sprague-Dawley rats (5 males, 5 females/group). The highest dose administered was 4217 mg/kg. The combined oral LD_{50} (males + females) was 3354 mg/kg (95% confidence limit between 2834 and 3970 mg/kg). Abnormalities observed at necropsy of animals (2530 g/kg group) that were killed at the end of the study were described as occasional white foci (~1 mm x 1 mm covering 75% of the non-glandular gastric epithelium). At necropsy, there were no abnormalities in animals that received a dose of 3000 mg/kg or higher and were killed at the end of the study.

Results relating to the acute oral toxicity of Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle) are reported in a micronucleus test involving groups of 10 (5 males, 5 females per group) Swiss CD-1 mice. A single dose of the test substance (500, 1000, and 2000 mg/kg) was administered by gavage to the 3 groups, respectively. Two female mice and 1 male mouse dosed with 2000 mg/kg died. Results relating to acute oral toxicity of Capryloyl

Salicylic Acid (in 0.5% carboxymethyl-cellulose aqueous vehicle) were also reported in an unscheduled DNA synthesis test using groups of 4 Sprague-Dawley rats. Single doses of 500, 1000, and 2000 mg/kg were administered by gavage, and no mortalities or clinical signs were observed.

A short-term (10 day) dermal toxicity study on Capryloyl Salicylic Acid (in PEG-6) was performed using groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain. The test substance was applied for 6 h directly to the back once daily at concentrations of 2% and 5%. The NOEL for local and systemic effects was considered to be 2% and > 5%, respectively. Results relating to short-term dermal toxicity of Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) are reported in a guinea pig maximization test involving 20 Dunkin-Hartley guinea pigs. One animal was found dead on day 18, but microscopic examination revealed no apparent abnormalities.

A short-term (28 day) oral toxicity study on Capryloyl Salicylic Acid (PEG-6) was performed using groups of 10 or 20 rats of the CRL:CD(SD)BR strain. The highest dose group (initially 300 mg/kg/day) consisted of 20 rats (10 males, 10 females per group). Each of the remaining dose groups (10, 30, and 100 mg/kg/day) consisted of 10 rats (5 males, 5 females per group). The NOEL for local effects was 30 mg/kg/day, and the NOEL for systemic effects was > 100 mg/kg/day.

The developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 24 pregnant female Sprague-Dawley rats. The test material was applied for 6 h directly to skin on the back (not less than 10% of the body area). One group was dosed with 40 mg/kg/day and the other group was dosed with 100 mg/kg/day on gestation days 6 to 15. The NOAEL for developmental toxicity was established as 40 mg/kg/day, based on an increase in the incidence of fetuses with incomplete ossification of the sacral neural arch at 100 mg/kg/day. The NOAEL was not established for maternal toxicity, as treatment-related effects (local reaction at the site of administration and reductions in body weight gain) were observed at both doses tested. The reproductive and developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 10 male and 10 female Wistar Hannover rats. The animals were dosed orally (by gavage) with the test substance once daily. The 3 dose groups received 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day, respectively (dose volume of 4 mL/kg/day). Males were dosed for 50 days total and females were dosed for 40 to 49 days total. The NOEL was considered to be 100 mg/kg/day for the following: parental toxicity, embryo-fetal developmental toxicity, and pup development until day 4 post-partum.

In the Ames test, Capryloyl Salicylic Acid (in ethanol) was non-genotoxic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 uvr A when evaluated at doses up to 1000 µg/plate with and without metabolic activation. Capryloyl Salicylic Acid (in ethanol) was classified as clastogenic with, but not without, metabolic activation, in the mammalian chromosome aberration test involving Chinese hamster ovary cells. The test material was evaluated at concentrations of 50 µg/mL and 80 µg/mL in this assay.

Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) was classified as non-clastogenic when evaluated in in vivo micronucleus tests using groups of 5 male and5 female mice of the CD-1 strain. Single doses of the test substance up to 2000 mg/kg were administered by gavage. The in vivo unscheduled DNA synthesis test was also used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) using groups of 4 Sprague-Dawley rats. Single doses of 500, 1000, and 2000 mg/kg were administered by gavage, and the test material was classified as non-clastogenic.

When 3 male New Zealand White rabbits were patch tested with 0.5 g of Capryloyl Salicylic Acid trade, skin irritation was not observed. In addition to these results, skin irritation was reported in other types of toxicity tests. In a short-term dermal toxicity study, daily (for 10 days) applications of Capryloyl Salicylic Acid (in PEG-6) at a concentration of 5% caused very slight erythema and edema in a group of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain. In a developmental toxicity study, Capryloyl Salicylic Acid (in PEG-6) was applied to the backs of pregnant female Sprague-Dawley rats (2 groups of 24) at doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. Erythema and eschar formation, dose-related in severity, were observed (number of animals not stated).

Reactions described as cutaneous signs of slight intensity were observed in 5 of 49 subjects after application of a face product containing 0.3% Capryloyl Salicylic Acid to the face and eye contour twice daily for 4 weeks.

Three maximization tests involved groups of 20 Dunkin-Hartley guinea pigs tested with Capryloyl Salicylic Acid (different vehicles used). A challenge concentration of 2% was sensitizing to 5 of 20 guinea pigs, and a challenge concentration of 5% was sensitizing to 2 of 20 guinea pigs. The absence of skin sensitization was noted in a group of 20 guinea pigs challenged with a concentration of 1%. Additionally, findings relating to skin irritation (number of animals with reactions not stated) during induction were reported in the 3 maximization tests. Test concentrations of 1% and 25% applied topically were irritating, whereas, 0.5% (injected intradermally) and 10% (topical application) were not.

In 2 HRIPTs involving 106 subjects and 105 subjects, respectively, face serum products containing 0.5% Capryloyl Salicylic Acid was classified as a non-sensitizer. In the HRIPT involving 106 subjects, slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A cream product and a fluid cream product (each containing 0.5% Capryloyl Salicylic Acid) were also classified as non-sensitizers in HRIPTs involving 104 subjects and 106 subjects, respectively. A cosmetic product containing 2% Capryloyl Salicylic Acid was classified as a non-sensitizer in an HRIPT involving 102 subjects. Slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A face powder containing 2% Capryloyl Salicylic Acid and a deodorant aerosol product containing 2% Capryloyl Salicylic Acid were also classified as non-sensitizers in HRIPTs involving 105 subjects and 103 subjects, respectively.

Capryloyl Salicylic Acid was classified as being a severe ocular irritant in a test involving 3 New Zealand White rabbits. The test substance (~ 65 mg) was instilled into the eye, and exposure was not followed by ocular rinsing.

A face product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 49 subjects twice a day for 4 weeks. Clinical examinations revealed an ocular irritation rate of 0.03%. In another test, an eye contour product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 50 subjects twice a day for 4 weeks, and clinical examinations revealed an ocular irritation rate of 0.04%

Positive patch test reactions to 1% Capryloyl Salicylic Acid have been reported in case reports, one of which reported no reactions in a control group of 15 subjects.

DRAFT DISCUSSION

CIR published a safety assessment of Salicylic Acid and 16 salicylates in 2003. That safety assessment included Capryloyl Salicylic Acid because, at the time, it was mischaracterized and defined as an ester. However, it is now known that this ingredient is a ketone and it does not belong in that family of ingredients; therefore, a separate report has been prepared.

The Panel discussed the issue of skin sensitization potential for this ingredient. Capryloyl Salicylic Acid induced skin sensitization in guinea pig maximization tests at challenge concentrations of 0.5%, 2%, and 5%, but not at 1%. However, in HRIPTs, cosmetic products containing 0.5% or 2% Capryloyl Salicylic Acid were classified as non-sensitizing. After reviewing the HRIPT results and considering that the highest reported maximum use concentration of Capryloyl Salicylic Acid is 0.5% in leave-on cosmetic products, the Panel was reassured that the sensitization potential of exposure to this ingredient via cosmetic use is not a risk. Furthermore, dermatologists on the Panel stated that, based on their clinical experience, Capryloyl Salicylic Acid is not a sensitizer.

The Panel noted the absence of carcinogenicity data from this safety assessment. However, it was agreed that due to the predominance of negative genotoxicity data on Capryloyl Salicylic Acid and the absence of structural alerts in the chemical structure, the carcinogenic potential of this ingredient is not a concern.

The Panel also discussed the issue of incidental inhalation exposure from powders and hair sprays. The Council's survey results indicate that Capryloyl Salicylic Acid is being used in deodorant sprays (aerosolized) at concentrations up to 0.3%. Also, Capryloyl Salicylic Acid is being used in face powders at concentrations up to 0.3%. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. 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 https://www.cir-safety.org/cir-findings.

DRAFT CONCLUSION

To be determined.

TABLES

Table 1. Chemical and Physical properties of Capryloyl Salicylic Acid

Property	Value/Results	Reference
Capryloyl Salicylic Acid		
Form (at 20 ºC and 1013 hPa)	White powder	[3]
Molecular weight	264.32	[6]
Specific Gravity (at 23 ºC)	0.35	[3]
Boiling point (ºC)	thermal decomposition occurs (at 264ºC) before boiling	[3]
Melting/Freezing point (ºC) (at 101,325 Pa)	115	[3]
Water solubility (mg/L at 20 ºC)	29.7	[3]
Vapor pressure (Pa at 21 ºC)	97.3	[3]
log P_{ow} (at 20 ºC)	0.32 (non-ionized form)	[3]
pK_a (at 25 ºC)	2.68 ± 0.10 (estimated)	[6]

Table 2. Frequency (2019) and Concentration (2018) of Use According to Duration and Exposure.

	# of Uses	*Max Conc of Use (%)*
	Capryloyl Salicylic Acid	
	2019[8]	**2018[9]**
Totals*	**104**	**0.1 -0.5**
Duration of Use		
Leave-On	***93***	***0.1-0.5***
Rinse-Off	***11***	***0.1-0.4***
Diluted for (Bath) Use	***NR***	***NR***
Eye Area	9	NR
Incidental Ingestion	NR	0.1
Incidental Inhalation-Spray	35[a];28[b]	0.1
Incidental Inhalation-Powder	28[b]	0.3; 0.3-0.5[c]
Dermal Contact	104	0.1-0.5
Deodorant (underarm)	NR	not spray: 0.3 aerosol: 0.3
Hair - Non-Coloring	NR	0.1
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	0.1-0.3
Baby Products	NR	NR

*Because this 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]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c]It is possible that these products may be powders, but it is not specified whether the reported uses are powders.

Table 3. Genotoxicity Studies on Capryloyl Salicylic Acid.

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
		In Vitro		
Capryloyl Salicylic Acid (in ethanol)	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvr A.	Ames test, with and without metabolic activation. Test protocol equivalent or similar to OECD TG 471. Controls: vehicle (ethanol); positive, without metabolic activation (2-aminoacridine, 2-nitrofluorene, and sodium azide); and positive, with metabolic activation (2-aminoanthracene and 4-nitroquinoline-1-oxide)	1st experiment: doses up to 1000 µg/plate (with and without metabolic activation). 2nd experiment: doses up to 100 and 200 µg/plate (without metabolic activation)	No substantial increases in revertant colony numbers over vehicle control count in any bacterial strain. Non-genotoxic.[3]
Capryloyl Salicylic Acid (in ethanol)	Chinese hamster ovary cells	Mammalian chromosome aberration test, with and without metabolic activation. Controls: vehicle (ethanol) and positive (mitomycin C and cyclophosphamide). Exposure and harvest times not reported.	Two experiments performed at concentrations up to 50 mg/mL and 80 mg/mL, respectively.	1st test (with metabolic activation): statistically significant increases in chromosome aberrations at 1st harvest observed at 50 µg/mL. (actual frequency was within background for this cell line). 2nd test (with metabolic activation): statistically significant increases in chromosome aberrations at 1st harvest observed at 80 µg/mL (actual frequency was above background for this cell line). No statistically significant increases in chromosome aberrations without metabolic activation. Results for positive controls confirmed validity of the test system. Clastogenic to Chinese hamster ovary cells.[4]
		In Vivo		
Capryloyl Salicylic Acid (0.5% in carboxymethyl-cellulose)	Groups of 10 (5 males, 5 females per group) mice of the CD-1 strain	Micronucleus test. Protocol similar to OECD TG 474, with minor deviations. Vehicle control group dosed with carboxymethylcellulose, and positive control group dosed with mitomycin C (injected intraperitoneally). Animals killed at 24 h, 48 h, and 72 h post-dosing. Bone marrow cells obtained and analyzed for micronuclei. Minimum of 1000 polychromatic erythrocytes (PCE) counted per animal.	3 groups received single oral doses (by gavage) of 250, 500, and 1000 mg/kg, respectively.	Micronuclei not induced at any administered dose of test material, despite decrease in PCE/normochromatic erythrocytes at dose of 1000 mg/kg at 24 h. Test material was non-clastogenic. Positive control induced appropriate increase in number of PCE.[3]
Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose)	Groups of 10 (5 males, 5 females per group) Swiss CD-1 mice	Micronucleus test. Performed in accordance with OECD TG 474. Vehicle control group dosed with carboxymethyl-cellulose, and positive control group dosed with mitomycin C.	3 groups received single oral doses (by gavage) of 500, 1000, and 2000 mg/kg), respectively.	A slight increase in the polychromatic erythrocytes (PCEs)/normochromatic erythrocytes (NCEs) ratio was observed in males of the 2000 mg/kg dose group, only at the 24-h sampling time. No statistically significant increases in frequency of micronucleated PCEs. Test material was non-clastogenic. Positive and negative controls yielded satisfactory response, confirming validity of test system.[4]

Table 3. Genotoxicity Studies on Capryloyl Salicylic Acid.

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose)	Groups of 4 Sprague-Dawley rats	Unscheduled DNA synthesis test. Performed in accordance with OECD TG 486. Vehicle control group dosed with carboxymethylcellulose, and 2-acetamidofluorene and methylnitrosourea served as positive controls.	In 2 tests, single doses of 500, 1000, and 2000 mg/kg were administered by gavage. In the 2 tests, animals were killed at 14 h and 2 h, respectively.	Treatment with the test material did not produce group mean net grain value that was greater than -0.88, and no more than 6% of the cells were found in repair. Test material was non-clastogenic. Positive and negative controls yielded satis-factory response, confirming validity of test system.[4]

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Irritation (Animal)			
Capryloyl Salicylic Acid	3 male New Zealand White rabbits	OECD TG 404. Occlusive patch containing test material (0.5 g moistened with distilled water (0.5 ml)) applied for 4 h to 62.5 cm^2 area on dorsal flank. Skin irritation evaluated according to Draize scale at 24 h, 48 h, and 72 h after patch application.	No skin irritation at any time after patch application. Test material classified as non-irritant.[3]
Capryloyl Salicylic Acid (in PEG 300) tested at concentrations of 2% and 5%.	5 female rats of the Crl:CD(SD)BR (VAF plus) strain	Test protocol similar to OECD TG 410. Applied for 6 h directly to the back (not less than 10% of body area; constant volume of 2 ml/kg) once daily (for 10 days) at each concentration	In group that received 5% concentration, very slight erythema observed in 2 to 5 animals throughout dosing period (beginning at day 6), and well-defined erythema observed in 1 female between days 8 and 10 of dosing period. Very slight edema observed in 3 or 4 animals treated with 5%, beginning at day 7, and scabbing (minimal/moderate; observed at necropsy) at application site observed in all animals treated with 5%.[3]
Capryloyl Salicylic Acid (in PEG-6)	2 groups of 24 pregnant female Sprague-Dawley rats	Developmental toxicity study in which skin irritation results are included. Test material applied to skin of the back (2 groups) at doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15.	Erythema and eschar formation observed in both groups (number of animals not stated), the severity of which was dose-related. Slight edema also reported, and scabbing and/or reddening at test sites observed at necropsy.[3]
Irritation (Human)			
Face product containing a 0.3% Capryloyl Salicylic Acid	49 subjects	Product applied to face and eye contour twice a day for 4 weeks.	Cutaneous signs of slight intensity were observed in 5 subjects.[4]

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Sensitization (Animal)			
Capryloyl Salicylic Acid (in arachis oil), tested during induction (1% and 0.5%) and challenge (2%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	OECD TG 406. Guinea pig maximization test. Initially, following 3 pairs of intradermal induction injections (0.1 ml per injection) made in group of 20animals: 1:1 mixture of Freund's complete Adjuvant in distilled water; 1% (w/v) dilution of test material in arachis oil; and 1% (w/v) dilution of test material in a 1:1 preparation of Freund's complete Adjuvant and arachis oil. These intradermal injections comprise 2 induction exposures during an exposure period of 7 days + 48 h. One week later, a 48-h topical application (induction) of 0.2 to 0.3 ml of 0.5% (w/w) test material in arachis oil over injection sites (shoulder region). At 2 weeks post-topical induction, a 24-h epicutaneous challenge with 2% (w/w) test material in arachis oil (occlusive patch) involved the left flank. Dose per cm^2 for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h. Positive and vehicle controls were 2,4-dinitrochlorobenzene and arachis oil, respectively.	Positive reactions observed in 14 of 20 guinea pigs at 24 h after challenge. At 48 h, 4 guinea pigs had positive reactions. Test material classified as skin sensitizer because more than 30% of total number of guinea pigs tested (i.e., 70%) had positive response. Control animals treated with arachis oil did not have positive reactions. Positive control (2,4-dinitrochlorobenzene) induced sensitization.[3]
Capryloyl Salicylic Acid (in ethanol), tested during induction (10% and 0.5%) and challenge (2%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	Method similar to OECD TG 406. Guinea pig maximization test. During induction, animals injected intradermally with concentration of 0.5%, and received topical applications at a concentration of 10%. Challenged with a concentration of 2%. The dose per cm^2 for induction and challenge applications was not stated. Challenge reactions were scored at 24 h and 48 h.	No signs of skin irritation during induction at concentrations of 0.5% (injected intradermally) and 10% (topical application). Positive (sensitization) reactions observed (at 24 h and 48 h) at the application sites of 5 guinea pigs. Classified as limited evidence of reactions indicative of skin sensitization. Adverse skin reactions not observed in control animals.[4]
Capryloyl Salicylic Acid (in PEG 300), tested during induction (25%, 15%, and 10%) and challenge (5%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	OECD TG 406 (no significant protocol deviations). Guinea pig maximization test. During induction, test material applied topically at concentration of 25%. Due to severity of skin reactions after first induction application, concentration reduced to 15% for 2^{nd} induction, and to 10% for last induction. Animals challenged topically with a test substance concentration of 5%. Dose per cm^2 for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h.	When a concentration of 25% was applied, several test animals (number not stated) had erythema scores of 2 or more at the application site after the first induction application. At 24 h, positive (sensitization) reactions observed at application sites of 2 animals. Positive reactions not observed in any animals at 48 h. Reactions classified as limited evidence of reactions indicative of skin sensitization. Adverse skin reactions not observed in control animals.[4]
Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose), tested at 1% (induction and challenge)	Dunkin-Hartley guinea pigs (test: 10 males, 10 females; controls: 5 males, 5 females)	OECD TG 406. Guinea pig maximization test. Topical application during induction, followed by topical challenge. Dose per cm^2 for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h. Ten positive control animals tested with 2,4-dinitrochlorobenzene.	Skin reactions not observed in any test animals during induction or challenge. No evidence of adverse skin reactions in negative control animals. Test material classified as non-sensitizer. Sensitization in 3 of 10 positive control animals.[4] [Results relating to short-term dermal toxicity in that section of this report.]

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
		Sensitization (Human)	
Face serum product containing a 0.5% Capryloyl Salicylic Acid	106 subjects	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm^2 area; application site not stated) 3 times per week (Tuesdays, Thursdays, and Saturdays) for total of 9 applications. Patches removed after 48 h (or 72 h for patches applied on Saturday). Sites graded 15 to 20 min after patch removal. Challenge phase initiated after 13-day non-treatment period. Challenge patch containing 0.02 mL of product applied to previously treated site and to new site for 48 h. Patch alone applied to new site served as negative control. Reactions scored at least 30 min and ~ 48 h after patch removal.	Slight skin irritation observed in a few subjects (number not stated) during induction phase and at first challenge reading. Sensitization not observed at 1st challenge reading, and no adverse responses observed at final challenge reading. Product classified as non-sensitizer.[4]
Face serum product containing a 0.5% Capryloyl Salicylic Acid	105 subjects.	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm^2 area; application site not stated) 3 times per week (Mondays, Wednesdays, and Fridays) for total of 9 applications. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 10 to 14-day non-treatment period. Challenge patch containing 0.02 ml of product applied to previously treated site and to new site for 48 h, after which reactions. Reactions also scored at 72 h and 96 h post-application.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer.[4]
Cream product containing a 0.5% Capryloyl Salicylic Acid	104 subjects	HRIPT. Occlusive patches containing 0.02 mL of product applied to 50 mm^2 area. Details relating to test protocol not included.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer.[4]
Fluid cream product containing a 0.5% Capryloyl Salicylic Acid	106 subjects	HRIPT. Occlusive patches containing 0.02 mL of product applied to 50 mm^2 area. Details relating to test protocol not included.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer.[4]
Cosmetic product containing a 2% Capryloyl Salicylic Acid	102 subjects	HRIPT. During induction, semi-occlusive patches containing 0.2 mL of product applied (40 mm^2 area; application site not stated) 3 times per week (Tuesdays, Thursdays, and Saturdays) for total of 9 applications. Patches removed after 48 ± 4 h (or 72 ± 4 h for patches applied on Saturday). Sites graded 15 to 30 min after patch removal. Challenge phase initiated after 13-day non-treatment period. Challenge patch containing 0.2 ml of product applied to previously treated site and to a new site for 48 ± 4 h. Patch alone applied to new site served as negative control. Reactions scored 30 to 35 min and ~ 48 ± 4 h after patch removal.	Slight skin irritation observed in a few subjects (number not stated) during induction phase and at first challenge reading. Sensitization not observed at 1st challenge reading, and no adverse responses observed at final challenge reading. Product classified as non-sensitizer.[4]

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Face powder containing a 2 % Capryloyl Salicylic Acid	105 subjects	During induction, occlusive patches containing 0.02 mL of product applied (50 mm^2 area; application site not stated) 3 times per week (Mondays, Wednesdays, and Fridays) for total of 9 applications. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 10- to 14-day non-treatment period. Challenge patch containing 0.02 ml of product applied to previously treated site and to new site for 48 h, after which reactions scored. Reactions also scored at 72 h and 96 h post-application.	No evidence of adverse responses during induction or challenge phases. Product classified as non-sensitizer.[4]
Deodorant aerosol product containing a 2% Capryloyl Salicylic Acid	103 subjects	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm^2 area; application site not stated) 9 times over period of 3 consecutive weeks. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 2-week non-treatment period. Challenge patch containing 0.02 ml of product applied to previously treated site and to new site for 48 h, after which reactions scored. Reactions also scored at 72 h and 96 h post-application. Patch alone applied to new site served as negative control.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer.[4]

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2019 VCRP Data

Capryloyl Salicylic Acid

03D - Eye Lotion	5
03G - Other Eye Makeup Preparations	4
07I - Other Makeup Preparations	1
11G - Other Shaving Preparation Products	2
12A - Cleansing	9
12C - Face and Neck (exc shave)	24
12D - Body and Hand (exc shave)	4
12F - Moisturizing	24
12G - Night	10
12J - Other Skin Care Preps	20
13C - Other Suntan Preparations	1
Total	**104**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: May 23, 2019

SUBJECT: Draft Report: Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics (June meeting draft)

The Council respectfully submits the following comments on the draft report, Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics.

Chemistry - It is not necessary to repeat the earlier mistake in the Dictionary that is presented in the Introduction. Presenting the error in the Introduction and Summary should be sufficient. The Chemistry section should focus on the ingredient that is being reviewed.

Cosmetic Use - Please correct "baring" to "bearing". The last paragraph of this section should be deleted as this information is also presented in the previous paragraph.

Clinical Studies - Please correct: "path" to "patch"

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org