ADMIN

Strategy Memo:
Fatty Amphocarboxylates

EXPERT PANEL MEETING
December 2 - 3, 2024

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, M.S., Senior Scientific Analyst/Writer
Date: November 8, 2024
Subject: Strategy Memo on Fatty Amphocarboxylates

Enclosed is a strategy memo for the Panel's review regarding Fatty Amphocarboxylates. At the June 2024 meeting, the Panel reviewed the Revised Draft Report on the 11 fatty amphocarboxylates, along with justification tables on potential read-across substances, and issued an Insufficient Data Announcement (IDA). In order to conclude on the safety of these ingredients, the Panel requested the following data:

- Dermal absorption data
- DART data on Disodium Cocoamphodiacetate
- Further information regarding the composition and impurities of these ingredients as cosmetics (particularly percentage of actives in ingredients and fatty acid compositions)
- Sensitization data on Sodium Lauroamphoacetate at maximum use concentration
- Sensitization data on Disodium Lauroamphodiacetate at maximum use concentration

Since the issuing of the IDA, quantitative structure-activity relationship (QSAR) skin sensitization predictions on C12 diacetate 1, C12 diacetate 2, C12 monoacetate 1, and C12 monoacetate 2 have been received from the REACH Amphoacetates Consortium (*data1_FattyAmphocarboxylates_122024 – data_5_FattyAmphocarboxylates_122024*). In addition, the Consortium stated that a prenatal developmental toxicity study in rabbits performed using C8-18 (diacetate form) is currently underway and would likely be finalized by the end of April 2025. Accordingly, the Consortium proposed that the Expert Panel table this assessment until June 2025 to ensure all information has been received prior to the next review of this report.

The Read-Across Working-Group (RAWG) is thus being asked:

1. Are the QSAR skin sensitization predictions on C12 diacetate 1, C12 diacetate 2, C12 monoacetate 1, and C12 monoacetate 2 appropriate for inclusion in the report? Previous deliberations (transcripts_FattyAmphocarboxylates_122024) are provided herein. Do these data help to fill the state gaps for sensitization of Sodium Lauroamphoacetate and/or Disodium Lauroamphodiacetate?

The Expert Panel is being asked:

2. Would the Panel like to table this report, as proposed by the Consortium, to allow for all information to be received prior to the next review of this report?

2a. What is the Panel's deadline for which receiving these data?

JUNE 2023 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – June 12, 2023

DR. BELSITO: Okie doke. So, amphocarboxylates. So, I guess that the first order of business with this is are we -- sorry. Amphocarboxylates. So, the first order of business, are we okay with changing the name from amphoacetates to include the propionates? Yes.

DR. RETTIE: I think so.

DR. BELSITO: Okay. And we're happy with the name amphocarboxylates?

DR. RETTIE: Good enough for me.

DR. BELSITO: Okay. And then so basically this was a 2021 priority on how we reported frequency of use for Sodium cocamphodiacetate and then it turned out there were four other amphoacetates. Disodium cocoamphodiacetate, disodium cocoamphodipropianate, sodium cocoamphoacetate and sodium cocoamphopropionate that were up for review soon.

And so that brought it to five ingredients and then there were a bunch of others that we felt we could read across that were in the dictionary hanging out there. So, this created this group of what's now called amphocarboxylates. We had a huge, huge Wave 2 data dump, in part because it appears that the ECHA data on C12 though C14 amphoacetates, C12 amphoacetates and C8 through C18 amphoacetates may or may not have been brought into this document if I have it right.

And so, the question is do we have -- and then as part of that data dump, we were told that there is going to be some DART studies that are coming out, that we would have maybe in 2024 or 2026. There is DART data that -- one DART study that suggests cardiac defects but then this association had someone -- I forget the name of the company -- review all of the DART data and come up with the idea that this was not real and most of the DART data did not show any of those effects.

I think the bottom line is where are we going with this? Are we tabling it so that the writers can go back in and figure out what's duplicative between Wave 2 and what we saw in the original report? If we table it, are we going to wait until we get this additional repo data in 2024, or are we going to just table it to incorporate all the data we have now and see.

Because, quite honestly, from my review and I, obviously, have a huge question to Paul, is what you thought about the DART data and they thyroid effects? Those were the only issues that I really saw.

DR. SNYDER: Well, it's concerning. But, again, if there's additional data with better NOELs and things like that, I definitely want to see them. We should see them. I mean, we typically default to where we don't like to table things because otherwise they go on forever. So, I think we just need to push forward with what we want and what we need.

DR. BELSITO: I guess, but -- well, first there are some questions to us. So, why don't we go through the questions and then we can decide. These are all in Wave 2.

Do we agree that the data are directly applicable to the ingredients under review in this report? And obviously they are. This is the C8 through 18. This is that ECHA data. You didn't think so?

DR. RETTIE: I have a lot of questions about the composition of what we're looking at here, relative to the European read across REACH data. When I read that, the REACH data, in some detail, and it took me a long time. It was quite good, they provided you a synthetic scheme, I looked at the synthetic scheme. It appeared that the synthetic scheme from the European data was the same as what was being used for our ingredients in this report.

In the European data they refer to these -- it doesn't matter which group it is, C12 to 14, C10 to C18. It appeared to me that they were referring to mixtures of the monoesters with some diesters, with some ether products as well in the European set. And they provide you some structures for that. It appeared to me that that was a consequence of the synthetic methodology, and so that's all fine.

In our report there did not appear to be any mention of monoacetate and diacetate mixtures within a given ingredient. And there was no mention of ethers. So just in a very bird's eye view from this, it seemed like apples and oranges.

Are we to take from our report that the purification methodology used here are so superior to the difficulties that it seemed like our European colleagues had in making any kind of fraction, that when I look at the table structures that's a hundred percent that thing, whether it's the monoacetate, I didn't think so. But it's not here and I thought that was --

DR. BELSITO: The ECHA dossiers are coming from companies who manufacture these products, which suggested to me that these are impurities in cosmetic products.

MS. EISENMANN: I believe it's all the same information, they just provided much more information about composition in their submission.

DR. BELSITO: I agree.

MS. EISENMANN: That is in the ECHA dossier that does need to come into the report.

DR. RETTIE: Okay.

MS. EISENMANN: Because they were very specific on what that composition of each material that was tested, and it's going to be hard to determine is it this study and whatever. We're going to have to try to look up -- if they put the trade names into the dossier that might help.

MS. CHERIAN: Sometimes they did and then I -- sorry. When they provided the trade names it was easier to see what they were actually testing. Because I can go back and look at a TDS or an SDS to see what it is.

MS. EISENMANN: Well, and to their submission, too. Because they used the trade names in the submission.

DR. RETTIE: Thanks. That's helpful.

DR. BELSITO: Yeah, I mean, ECHA data is all industry. Industry is submitting it to the European commission to meet REACH documentation.

MS. EISENMANN: I think the consortium that submitted the stuff to our submission is the same group that did the ECHA dossier.

DR. BELSITO: Probably. More than likely.

DR. RETTIE: But for sure our report needs some substantial updating to reflect what we're looking at here. And the language in the document needs to describe that these are mixtures of all of these different chemical components under an ingredient. That's not clear at all from what we're looking at right now.

DR. BELSITO: Okay. So, we are going to incorporate that. Your first question as a yes. And then does the panel feel that the data in the draft report should be altered to reflect the data presented in this submission? Yes. Responses to CIR data. Oh, dermal absorption data on dodecylamidopropylbetaine potential read across ingredient. I had a question to you, Allan, for that.

DR. RETTIE: Well, I didn't feel comfortable with that. The betaine is a quaternary compound, permanently charged, going to have different distribution, I'm sure. So, for that one I would say no. And I understand that the panels looked at betaine derivatives previously in a separate report. And if that were true, I thought that was where they belonged for the betaines.

DR. BELSITO: So, the answer from us is that, no we should not be using this as a potential read across?

DR. RETTIE: Not from me for betaine.

DR. KLAASSEN: I agree with you that the quaternary is a -- that's really different chemistry.

DR. BELSITO: Okay. So, we're not doing that.

DR. RETTIE: But there's three bullet points there, Don. The Betaine's just the first one I'm looking at. There's three questions about the read across there beyond the betaine. There's another two.

DR. BELSITO: Right.

DR. RETTIE: So, the last one, the N-(2-Hydroxyethl, blah, blah, blah, ethyl beta alanine, I thought that one was okay. It's a shorter chain length than the ones we're looking at right here, but it seemed to me that was fair game for read across.

DR. BELSITO: And where are you here, Allan?

DR. RETTIE: I'm on PDF 5.

DR. BELSITO: Okay.

DR. RETTIE: Of Wave 2.

DR. BELSITO: Yeah. Can we just go through the questions in order? Because there are questions before that I thought.

DR. RETTIE: Oh, there are?

DR. BELSITO: Yes.

DR. RETTIE: Apologies.

DR. SNYDER: What page are you on?

DR. BELSITO: I'm still on PDF Page 3. So, we're not going to allow unto -- we're not going with dodecyl amino. And then PDF Page 5. Yeah, okay. Sorry. The question is does the panel agree that the amphoacetate C8 - 18, C12 - 14, and C12 directly correlate with the listed ingredients above? And I think we've settled that, correct? We agree? Um, okay. So now you're up with the read across.

DR. RETTIE: Okay. So, we've done the betaine, we've decided no. Then there's one I'd like to come back to, the second one, because I'm not sure about that one.

The third one is the hydroxyethl beta alanine. That's the one that looks like it's a good read across. It's a shorter alkyl chain length than the ones that are listed, but it looks like a decent read across. They'll be some differences but it's very close. So, I would say okay on the third one.

I'd like to hear what others say about number two. This is an unsaturated group of alkyl derivatives. Maybe it's okay. I'm sort of on the fence about it a little bit. It's a maybe for me.

DR. BELSITO: Don't look at me. I don't have a clue.

DR. RETTIE: Did you have any thoughts about that one?

DR. KLAASSEN: No. Let's see what the other group says.

DR. RETTIE: See what Dr. Ross thinks? I think it could probably be pulled in, but he might have some other comments.

DR. BELSITO: So basically, dodecylamidopropylbetaine, no. N-(2-hydroxyethl)-N-[2-[(1-oxooctyl)amino]ethyl-beta-alanine, yes. And the middle one that I won't read is basically we're going to discuss tomorrow.

Okay. Are the data in the draft report along with information provided in Wave 2 efficient for the panel to determine the safety of the ingredients? If not -- essentially, we're being asked our list. And, I mean, I guess it's always hard. I spent a lot of time -- even though repro isn't my area of expertise -- reading through that whole document that they had that company -- and I'm blanking on the company's name.

DR. SNYDER: Colonial? Was it Colonial?

DR. BELSITO: No, it wasn't Colonial. They had an outside company.

MS. FIUME: Exponent.

DR. BELSITO: Exponent -- yes. Look at all of the data and come up with a conclusion that there were no developmental or reproductive toxic effects. And that this one study where there were cardiac effects on the infants was -- I don't know -- serendipity's not the right word, but asperous. And the other where there was a 300 milligram per kilogram effect on maternal was because something was going on in the thousand milligram group and it ended up killing those dams ahead of time, which gave that NOAEL.

But this is not my area, so I was throwing it back to you because that really seemed to be the only major issue that popped up in reading these about safety. But then they turn around and say that they're doing these huge studies that aren't going to be ready until 2024-2026. And why are they doing them if they have all of -- I mean, there's a good amount of DART data already. And there's just that one study and they had an outside group review it that came up with a conclusion that there were no DART effects from these as used.

So where are we going with this? You know, I mean, are there insufficiencies? Do we want to go ahead and say sufficient as used, but flag this for 2024 and 2025? Because right now there's no opinion on these at all, right, except for the four that we previously had reviewed and said are okay. And one of those is an ingredient in question in terms of a DART effect.

I mean, I've never been faced with an issue like this where the data looks clean but then they're promising to do these two other studies that are dangling out there.

MS. FIUME: So, Don, I'm not sure if it's the same company. But if it is, it's been since 2020 that we've been told that we'd be getting the DART studies. So, it's been almost three years and we haven't received those studies yet. And I don't know if that matters in your consideration on how to handle the report, but it's been since 2020 that we first received an email saying that DART studies would be ongoing.

DR. BELSITO: But it's entirely possible, like many other studies, that they were delayed because of the pandemic.

DR. SNYDER: So those additional studies, are they DART studies? Do we know?

DR. BELSITO: Yes.

DR. SNYDER: They wouldn't be running DART studies if they didn't --

MS. EISENMANN: One's a rabbit. So, they haven't done any rabbits. All of them are in rat and then there's the one gen.

DR. SNYDER: Okay. I mean, I tried to go to that Reference 4, and they don't have it -- I can't see that study. It's that ECHA dossier, so. Do we have that actual study that is referenced to --

DR. BELSITO: With the cardiac effects?

DR. SNYDER: Yeah.

MS. FIUME: If it was an unpublished study we only have the summary information that's in the dossier.

DR. SNYDER: Yeah.

DR. BELSITO: Yeah.

DR. KLAASSEN: I mean, these DART studies don't take five years. I mean, they're relatively short studies. Why it's taken them two or three years already and they're saying another couple years.

DR. SNYDER: It can take quite a long time, I mean, to get them finalized. Yeah, because they're big datasets and it just takes time. Yeah. It doesn't take long to run the study, but to finalize it and to end up with the conclusion, particularly a NOAEL and things like that, so.

DR. BELSITO: I mean, COVID has significantly affected, obviously, human clinical studies much more than animal studies, but it's affected everything. I mean, the labs at Columbia were essentially closed for 18 months. You know, animals died because they weren't tended to.

Some of these basic researchers essentially had to restart their lab all over again. So, they lost -- they had 12 - 14 months and then it took them another 12 months to get retooled. I mean, that doesn't bother me. If we were told in 2020, and we're sitting here in 2023, then, yeah, I can accept that it was COVID that did that.

But the question is, is there enough concern that we want that data in the absence of your being able to see that one study and the Exponent review of all the other DART studies that were there? I don't know if you went through all that, Paul?

DR. SNYDER: I did not because it came in a Wave that was --

DR. BELSITO: So, maybe the best approach here then is to table this. To go in and try and sort out what data came in under the ECHA dossiers that may have been duplicated in our original. Put it all together.

You know, have that Exponent -- because I thought that was -- I mean, to me, and it may have been all BS because you could BS me in that DART data, it's not my area of expertise, so I'd like to see what other people think. Bring that response back may be helpful.

There are a few other questions before we end this. So, it -- on PDF page 13 -- again, this is all Wave 2. I just worked off of Wave 2. It says, "it should be noted that these ingredients may contain amidopropyl dimethylamine." And then they said, also known as amidoamine. And the response from the manufacturer was that this was not -- amidoamine is not amidopropyl dimethylamine but dodecylamide N12 2-hydroxyethl amino ethyl. So, Allan, is that true?

DR. RETTIE: I did not read that far into Wave 2. Unfortunately, I went through Wave 1, so I can't answer that one right now.

DR. BELSITO: Okay. So that would need to be addressed.

DR. RETTIE: Yeah.

DR. BELSITO: I have a note that the composition impurities need to be updated based on the REACH registration, which I think is probably more accurate than what we had. But it's a good point, Monice, about matching up the trade names.

On PDF Page 15 -- again, I'm working all off of Wave 2. I was fortunate enough not to do this until Wave 2. So, PDF 15 of Wave 2, Priya, it's the fourth line down where we're talking about sodium lauroamphoacetate. You have 183 rinse off's and 17. It should be leave-ons, not rinse-offs.

And of note, there are new uses for these in baby products, so as you go over that. I don't know that I had any other comments. Thanks, Curt.

Oh, Wave 2, PDF 20. The third line from the bottom. If you could just check, Priya. It says, "patch testing was performed in 40 healthy volunteers and 488 topic subjects (affected by atopic dermatitis, psoriasis, or eczema). I mean, did they mean dermatitis subjects because, otherwise, they should've all had atopic dermatitis? Yeah.

MS. CHERIAN: I'll double check.

DR. BELSITO: Yeah. And the other thing to look into when we see this again, Paul, is this thyroid effect that I didn't think was real. But, okay. So, we're going to table it and what do you think, Monice, in December we'll see this again or --

MS. FIUME: I guess it depends on if we hear back. So, I have a question before you table it. So, is DART the only data need you have? I know there's questions about it but are there other additional data needs that if once the data that we received in Wave 2 get incorporated --

DR. BELSITO: Yeah. I actually went through it, and based upon my review of the Exponent analysis, and I was hoping to hear from Paul, I thought we could go safe as used when formulated to be non-irritating. That was my opinion.

Again, because I looked at what was reported or the Exponent analysis which seemed to be independent of this manufacturing group. So, I had no other data needs assuming that everyone was fine with the DART. But that was just me.

MS. FIUME: Okay. That's what I wanted to check.

DR. KLAASSEN: Exponent is a respectable company, so.

MS. EISENMANN: And it was John DeSesso who wrote it?

DR. SNYDER: Yeah. Yeah.

DR. BELSITO: Pardon?

DR. SNYDER: Yeah, I just didn't get that deep into that 115 data dump. I mean, it was just a huge data dump and I had already moved on to other ingredients. So, I can look at that tonight and if what they're reporting in that report, if I can agree with it, I think we can basically do what you say and go safe as used when formulated to be non-irritating.

DR. BELSITO: Okay. Why don't you do that, Paul.

DR. SNYDER: I mean, I still have some concerns why they're doing additional DART studies.

MS. EISENMANN: My guess is that ECHA required them.

DR. SNYDER: Okay. So that -- okay.

DR. BELSITO: Yeah. Because of that one study. Despite all the other negative studies. I mean, Europe has gotten very tough because they are moving very rapidly towards hazard-based. And genotox and reproductive tox, endocrine disruption, it's like there's no managing that hazard. You know, it's becoming very difficult. So that's -- yeah, they probably have accepted the fact that there was something spurious with that study, but they wanted some additional studies. You're probably right, Carol.

MS. FIUME: And, Don, in answer to your question on when it will come back, we'll just look at how it balances with the rest of Priya's workload and the other reports to see which report is better --

DR. BELSITO: Yeah. You got creamed.

MS. CHERIAN: I know. Lucky me.

MS. FIUME: Sorry. So, it's whether September or December will depend on some of that. Because there's a lot to put in. But knowing that prostaglandins will probably be December, we might try and balance it that way. But we'll have to just wait and see if that's okay.

DR. BELSITO: Yeah. That's fine. I mean, I think prostaglandins are probably more critical from my point of view, because we haven't looked at it and they're coming on the market and we don't know a lot about them. Whereas, these have been on the market for a long time and the data that I've seen, I think looks fairly good with these.

MS. FIUME: So, process wise, that's why it might be able to come back in September because we have those data, we just need to incorporate it. Prostaglandins analogues, we're waiting for additional data and you could put out an IDA, so that's why it'll probably skip a meeting.

DR. BELSITO: Okay.

DR. RETTIE: Can we briefly come back to the question you had about the amidopropyl? It's just clarification so I know what I'm looking up. So, there's a lot of amidopropyl dimethylamines. There's lauro, there's dodecyl. Is this one, one of those? Because if it's the lauro dodecylamine then it's very similar to the dodecanamide and I kind of have a sense of what's going on there. But amidopropyl dimethylamine is not really telling me anything.

DR. BELSITO: I'm sorry, Allan, I'm lost. Where are you and what comment?

DR. RETTIE: I'm back to the comment on Wave 2, PDF 13, the question about the known sensitizer, amidopropyl dimethylamine and the fact that the CAS number is something different.

DR. BELSITO: Okay.

DR. RETTIE: So, I'm just trying to get my head around the question, really. Amidopropyl dimethylamine is a little compound. Dodecanamide is a big compound. But when I try to find the amidopropyl dimethylamine, up comes a lot of different fatty acid chain lengths associated with that term.

So, there's a lauro one, there's an octododecyl one, and I'm suspicious that maybe they mean one of those. And maybe the lauro makes more sense. I just need some clarification.

DR. BELSITO: Yeah. Well, what I can tell you is that amidoamine is a starting material for the production of cocamidopropyl betaine. And when we were discussing that there are skin sensitization issues related to cocamidopropyl

betaine, and the question has been raised whether it's due to residual contaminants of amidoamine or dimethylaminopropylamine, DMAPA, which is formed to a lower extent during the production of cocamidopropyl betaine or whether it's the actual molecule itself.

And that came into our discussions, and I believe that our conclusion with cocamidopropyl betaine was formulated to be non-sensitizing with QRA or some other methodology. In our discussion, the issue of the impurity, the potential amidoamine or DMAPA impurities. That's my recollection and that's why I presume this was coming into play here. So, again, it's before your time so it's sort of thrown out of context, I know.

MS. FIUME: So, I believe the original reports on one of the original ingredients mentioned that aminopropyl dimethylamine -- let me make sure. Did this come from the original report -- no this was in a data sheet. It says amidoamine is an impurity. And so we flagged it as amidopropyl dimethylamine. Do I have that right?

MS. CHERIAN: Right.

MS. FIUME: Which according to the cocamidopropyl betaine report, is a sensitizer. The comment from the reviewer that submitted comments, they said that the MSDS refers to amidoamine which is not amidopropyl dimethylamine, but dodecanamide N-22 hydroxyethyl aminoethyl based on CAS number.

And so, what they're saying is that there's no skin sensitization available so it's not appropriate to call it a sensitizing impurity. If that makes sense. I think that's what I understand from it.

DR. RETTIE: So, their question's around just removing that language.

MS. FIUME: Right. Are we flagging it correctly as a possible sensitizer, impurity?

DR. BELSITO: So, they say that amidoamine is an impurity in their product, is that it? Because it says Reference 7, MSDS, refers to amidoamine cast, dah, dah, dah, dah, dah, which is not aminopropyl dimethylamine, but dah, dah, dah, dah, dah.

For this substance, and I didn't understand what this substance was, I presumed it was dodecanamide. It says no public information on skin sensitization is available, because quite clearly public information on skin sensitization of amidoamine is available because many patch test groups, including the North American, patch test with it and we see positive results. So, I don't know what they were referring to there.

MS. FIUME: Yeah. So, the MSDS is on sodium lauroamphoacetate. But since this tabled, we will delve into it to make sure that we have the correct impurity flagged and whether or not sensitization data is available on it. We'll take a look into the comment, and then when it comes back after the table, we'll have it clarified, if that's acceptable to the panel.

DR. BELSITO: Yeah.

MS. FIUME: Since there's so much question about exactly what it is.

DR. BELSITO: Mm-hmm.

DR. RETTIE: So, it was very helpful. I don't want to beat this to death, but what was very helpful in the ECHA documents was quite a reasonably clear picture of what their fractions contained, you know, all the way down to different percentages of the different fatty acids that were present in whatever you were starting from. Whether it was this coca product or not.

What we definitely don't have here, and what I think is pertinent to what we're talking about now when you bring up dodecanamide, and we've got saturation in the side chain, and then that comes back to whether we should include the second bullet point product and read across from an earlier question.

I'd just like to know what we know about the R groups for all the ingredients listed in Table 1. Maybe to the extent we can do that relative to how the ECHA document said about it. I did read the ECHA document, I didn't read all the Wave 2 because it came in late.

MS. FIUME: So, I think what happened, and Priya please jump in in case I have the history wrong. In trying to go through this ECHA dossier when they have those different chain lengths, they'll have three dossiers that actually have often the same information in each one and it's listed as read across or supportive data to the other. But I think what was done was we were trying to identify a one-to-one match, the ingredient to the chain length given, and didn't bring in those others. Do I have that correct?

MS CHERIAN: Right.

MS. FIUME: So, when they have the different chain lengths, sometimes it's difficult to figure out do they actually correspond to one of the ingredients or is it just equal to the general chain length? And I think that's what we tried to do on the first round, was to try to find the one-to-one match. So, we will bring in the rest of the information, and it may come into the report as a general chain length rather than a link to the specific ingredient, but to provide the information for you to use in the report overall.

DR. BELSITO: But we know that in general, I think, if you go back and look at the cocamidapropyl betaine report, you know, when you're getting into the coco derivatives, the chain lengths are not going to be uniform, they're going to be C12 to C18.

And we know from other reports that there's -- I mean, when you're looking at Peg 3 there's some Peg 2 and some Peg 4. When you're looking at lauro there's going to be -- you know, lauro theoretically is C12, but there's going to be some other chain lengths in there. It's not going to be pure.

And I think that's what you were seeing with the ECHA dossier. They were reporting a product that was lauro, but it was C10 to C12 or C12 to C14. But it's what they marketed as lauro.

MS. FIUME: So, we'll go back, and we'll readjust it I think. Like I said, I think they were trying to target. Now, my other question then -- question number two, if that's okay. When we received the information it was interesting because the one dossier says -- what's it called -- rationale for read across for REACH. Because they were giving chain lengths and they wanted it to read across to the different ingredients, which we've determined are probably actually are same ingredients, so it's not read across.

That middle point in the question two in Wave 2, that is a true read across. It doesn't look like it matches to our ingredients.

DR. RETTIE: See, that's my question.

MS. FIUME: We don't know that for sure. Okay.

DR. RETTIE: I'm not sure I know that for sure because everything that we've talked about for these acyl side chains so far, has been, I understand, for saturated fatty acids. And now the notion of maybe there's some unsaturated fatty acids out there that might be relevant, I don't know that.

So I think there's -- I mean, it's not a big difference. There are differences between unsaturated fatty acids and saturated fatty acids, certainly in the way the body deals with them. So, my main question was do we have any unsaturated fatty acids in our ingredients, if we ever get a composition to that level of detail?

And if we did, then I think bullet point two would be a read across, without any chatting with Dr. Ross.

MS. FIUME: So then, if it is then read across and not a match to the ingredient, my question was going to be in the past we've said if we have information on an endpoint we don't do read across. But would it still need to be brought in because it might -- based on chain length versus the actual ingredient?

DR. BELSITO: Which specific -- I mean, because I'm, again, lost. Where are you? PDF?

MS. FIUME: Let me find out which page.

DR. BELSITO: Is this Wave 2?

MS. FIUME: Yeah. So, Wave 2 in the memo, it's PDF Page 5, Question 2.

DR. BELSITO: Okay. This is was the read across question again.

MS. FIUME: So those last two bullets, if they're truly read across but you have the exiting --

DR. RETTIE: I think the last one's read across.

MS. FIUME: Okay.

DR. RETTIE: But I think bullet point two might be a match.

MS. FIUME: Might be a match.

DR. RETTIE: Might be a match if we know whether they're saturated or unsaturated fatty acids are in our ingredients, and we don't know that.

MS. FIUME: Okay.

DR. RETTIE: I suspect they are, but.

DR. BELSITO: I mean, the question is where do they want the read across? This may be weight of evidence to support -- I don't know where this is specifically going to go in. But where normally you might be looking at a read across is this one questionable DART study, and you have a bunch of other DART studies on your products that are negative, and you want to bring in some additional weight of evidence on read across materials. So that may be what they're looking at, in which case it would be helpful.

I mean, the more negative studies we have, if we have this one study with severe cardiac effects. It didn't say mild, right, they said severe. You know it might be nice to have as many studies as we can just showing we don't know why this happened in this one study. It seems to be spurious, and we have all of these other studies that are clean.

DR. SNYDER: What's our maximum concentration of use?

DR. BELSITO: It is 20 percent in rinse off and 5.4 percent in leave ons I believe.

MS. FIUME: And that's in other hair preparations.

DR. SNYDER: Thank you.

MS. FIUME: As far as dermal --

DR. BELSITO: I think it was 5.4.

MS. FIUME: The 5.4 is a hair --

DR. BELSITO: Okay.

MS. FIUME: -- preparation. I'm trying to think of what the dermal is. Do you have that handy?

DR. BELSITO: I didn't write it down here. It's in my notes but I have so many notes on these.

MS. FIUME: Yeah, that's why I keep flipping pages.

DR. BELSITO: I've never had so many sticky notes on one.

DR. RETTIE: I've got a 1.6 for dermal contact for disodium laurodiacetate, 1.6. No, I got 9.9 for disodium lauroamphoacetate for dermal contact.

DR. BELSITO: "Use 20 percent in a cleansing product, 5.4 in hair preparations, 1.3 in an eye makeup and 5.4 in baby shampoos." That's what I tagged. So, 5.4 in other hair preparations wouldn't be considered leave on.

MS. FIUME: It's leave on. I would just not -- I always classify that as dermal.

DR. BELSITO: Right. Okay.

MS. FIUME: And I didn't know if Paul wanted to know what the actual dermal contact was or --

DR. BELSITO: Yeah. Dermal contact -- what table is this in?

DR. RETTIE: I got Table 5.

DR. BELSITO: Yeah. This was fun.

MS. FIUME: It is used in other baby products at 1.6 percent.

MS. CHERIAN: And I think that's the highest dermal.

DR. BELSITO: I think I'm getting punchy.

MS. FIUME: It's too early. Yeah, so.

MS. BENNETT: Yeah, way too early, we haven't gotten to yeast yet.

DR. BELSITO: Oh, I know.

MS. FIUME: Oh my gosh, Priya.

DR. SNYDER: Well, this is the poster child of why we can't get these data dumps late in the game. Because this one is a clear result. It's just a lot to get through.

MS. FIUME: And we knew that, that's why we wanted to throw right out front that, do you want to table it because you think it's going to be okay? Or if you had additional IDA, we'll add that in but then bring it all back, so.

DR. BELSITO: You know, we'll see what Paul says after he reads.

DR. SNYDER: I've read the summary and the conclusion exactly. I mean, they did as thorough as I could possibly do in reviewing that data.

DR. BELSITO: Came to the conclusions --

DR. SNYDER: And the doses are very high. That's why you asked what's the concentration of use because they were at very high doses. And so, I do have some level of comfort with it on my initial review.

DR. BELSITO: I think we'll come in as safe as used when formulated to be non-sensitizing.

MS. FIUME: After it comes back from the table?

DR. BELSITO: Right. I don't have any additional data needs, and there's so much data here.

DR. SNYDER: The thyroids cup is not -- it's not --

DR. BELSITO: Okay. Let me just -- so we are tabling it just for organization. Is that a good word? No data needs currently. Likely safe as used when formulated to be non-irritating.

DR. RETTIE: So, you're presenting that tomorrow?

DR. BELSITO: Pardon?

DR. RETTIE: You're presenting that one tomorrow?

DR. BELSITO: I don't know. I haven't gotten that far.

DR. RETTIE: Oh, I have. You are.

Cohen Team – June 12, 2023

DR. COHEN: Amphocarboxylates. So, this is a draft report and this assessment is for 11 derived ingredients that are used as hair conditioning agents and surfactants. These are frequently used. Cocoamphodiacetate has the highest concentration of use in a rinse off product at 20 percent. And Disodium Lauroamphodiacetate has the highest concentration of the Leave-on product at 5.4 percent in a hair product.

It was noted that four related ingredients were reviewed by the Panel in 1990 and re-reviewed in 2008. That was the Disodium Cocoamphodiacetate, the Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate and the Sodium Cocoamphopropionate. And they would soon be considered for re-review.

Even though I think this was a draft report, we got to see it twice because in Wave 2, we got a large data load and a very large report. Of note, there was a mention of amidoamine as an impurity in Disodium Lauroamphodiacetate, which is an important sensitizer.

We have some irritation at sensitization. And we have some data on guinea pig maximization tests, but there's still some data needs. And, again, we have this large Wave 2. So, why don't I open it up for comments and then we can organize our thoughts for what our needs are. Tom, you want to start?

DR. SLAGA: Yes. Four of the ingredients, as you mentioned, were reviewed before and found safe and they were up for re-review. And so, they've been added to this report. And that's where most of the data is. Very little other data for the other. So the question is, can we read across from these four to the remaining ingredients and come up with a safe that way?

DR. COHEN: Yep. That was a question, what you guys think about read across on these?

DR. ROSS: Yeah, I got to the wrong page. This can't be right.

DR. SLAGA: It looks to me that it could be used for read across.

DR. COHEN: Wasn't there a comment about excluding the amphopropionates at one point?

DR. ROSS: There was some specific questions. Does the Panel agree that the data on the amphoacetate C8-18, amphoacetate C12-14, and amphoacetate C12 directly correlate to the ingredients above.

Second, should the data on the following potential read across sources be included in the report? Dodecylamidopropylbetaine, reaction products of 1 H-imidazole-1-ethanol -- and I'll leave the rest of that. And N-(2-hydroxyethl), (1-oxooctyl)amino]ethyl]-beta-alanine. So my reads on that specific Question 2, I don't know if you can read across from dodecylamidopropylbetaine, that's a zwitterion.

I mean, these things can be zwitterionic, but they're not necessarily in resting. I think you can read across from the reaction products of the imidazole and you can probably read across from the ethyl alanine.

With respect to the first question, yes, I think you can read across from the amphoacetates C8-18 and C12-14 to the appropriate structures. The betaine I don't know about. I don't know what other people's opinions, but if you just want to -- that's speaking to the read across. It's a long list of read across here. And, you know, my comments on this document were, if we do read across, it would be really nice to see where the read across came from with respect to the data and the document. Sometimes it's really difficult to look at this data and you don't know where it's coming from. But anyway, that's my comments on the read across. Most of it can be read across, there's maybe one you can't.

DR. COHEN: So, with regard to number one, we're going to include those? The data correlate to the ingredients listed.

DR. TILTON: I think a lot of the data is already included.

DR. ROSS: It is.

DR. COHEN: Well, it -- yeah. And we're okay with it?

DR. TILTON: I agree. Yeah.

DR. COHEN: And what about, Susan, Number 2?

DR. TILTON: I primarily agree with David. And I also don't know about the betaine, but since it's specific for read across for dermal absorption, it seems like we should probably not do that.

DR. COHEN: Probably not do what?

DR. TILTON: Use it for read across for dermal absorption data, for toxicokinetics, bioavailability.

DR. COHEN: It's not okay for dermal absorption and toxicokinetics.

DR. ROSS: That's the betaine, yeah.

DR. TILTON: Yeah.

DR. COHEN: Okay, three are the data in the draft report, along with the information provided sufficient for the Panel to determine the safety of this ingredient. That's what we have to talk about now.

DR. ROSS: Yeah.

DR. COHEN: So does the group feel that there's insufficient data at this point?

DR. ROSS: Yes. For me, I don't know about anybody else?

DR. COHEN: Yeah. So what do you have as a data need?

DR. ROSS: Well, I'd love the data in this document to agree all the way through. There was a lot of conflicting data in this document. And I think that comes from the nature of these compounds. You know, they're abbreviated in the ECHA document. It's UVCB, which is Unknown Variable Composition by materials. And so, I think that's where a lot of our problems are coming from. But despite that, I felt that you needed -- well, let's just go through it.

The DART was new data, the reproductive tox. And there was one study with Disodium Cocoamphodiacetate which showed severe cardiac abnormalities, but without a dose response. It was in all test groups, but without a dose response.

The second study looked just fine. And so, it's hard to know where to go with that. That was the subject of an Exponent consulting report, which was in the document. I think we can talk about whether we need additional DART data on this compound, tested to be the highest purity possible, whether or not that's justified or not.

DR. COHEN: So DART on?

DR. ROSS: This compound would be Disodium Cocoamphodiacetate. It's the first one on the list. That's where you had the two conflicting studies, the cardiac and the visceral malformations in one study and not in the other. So that's my first issue. I thought we should discuss that, whether or not we needed it. The Sodium Lauroamphoacetate, the new compound, if you like, the DART there was just fine.

The other issue was the dermal irritation and sensitization, in particularly, the sensitization with Sodium Lauroamphoacetate. It's fine with the other original four compounds that were in the previous document. But there was no -- the only HRIPT data I could see was at 0.5 percent, the Sodium Lauroamphoacetate.

DR. COHEN: And this goes to (inaudible). And this is way below max use.

DR. ROSS: Max use is 9.9 percent. So yeah. And then, ocular I think is okay since we've got 5 percent and max is 1.3 percent. So, I guess it's HRIPT on Sodium Lauroamphoacetate and this issue of the DART. That's my summary on it.

MS. CHERIAN: We are expecting more DART data, I think by 2024, 2026. Bart, do you remember?

DR. ROSS: Yeah, that was another comment I had. It's coming, but I don't know if you want to wait that long.

DR. COHEN: Will it be within the two year window of this report? So, I don't know. Does it matter if it comes in safe?

DR. ROSS: Yeah, my dates say April 24, and then generic 2025. Oh, just while I'm talking here. Exponent, you know, in their report they did have additional rats that they -- rat citations that they considered that we didn't have in a report.

MS. CHERIAN: Okay. I'll take a look at that.

DR. ROSS: And another one did flag cardiac malformation. That was the Viends, V-I-E-N-D-S, Viends, 2022b. But it was very low incidence and I feel it should be in.

DR. TILTON: So I had also noted missing dermal absorption data and information on toxicokinetics without the read across.

DR. COHEN: Yeah, for the (inaudible)? No? Or are we talking about something else?

DR. TILTON: Well, just that there is no dermal absorption data for any of these.

DR. COHEN: Got it.

DR. TILTON: That was only going to be provided through read across. So in terms of the DART, there were severe cardiac effects noted, but they were independent of those. And I was trying to find where I made this note, but in the Wave 2 it was concluded that those were not treatment-related effects.

DR. ROSS: That was in the Exponent consulting report.

DR. TILTON: Oh, okay.

DR. COHEN: How did they come to that conclusion?

DR. ROSS: I think it was primarily because there was no dose response.

DR. COHEN: What if you're above the dose from the lowest dose?

DR. ROSS: That was their conclusion.

DR. COHEN: Okay.

DR. ROSS: And it may be a reasonable conclusion. Usually you're looking for some sort of dose response. But yeah, there are times when you may not see it.

DR. COHEN: Retinoids don't have a clear dose response to teratogenicity.

DR. ROSS: I mean, it was a flag -- it was that one study plus the additional study in the reports. And the other study was clean, so just how you interpret that.

DR. COHEN: And the control group didn't have them, right?

DR. ROSS: Correct.

DR. TILTON: That's correct.

DR. COHEN: So that's a rub. Okay. So we're going to have an IDA, right? Tom, you have a list of insufficiencies that you want to list.

DR. SLAGA: If you're talking to me, you broke up.

DR. COHEN: Yeah. Everyone here, for an IDA, has some things they want to add. Do you have anything in particular you want to enumerate? Because It's time that we just get --

DR. SLAGA: Yeah. Well it’s no problem because it's a draft report. So, IDA is fine.

DR. COHEN: Yeah. Any specifics?

DR. SLAGA: (Inaudible) some of them can stand alone.

DR. COHEN: Okay. And items in particular? Or we will run through the group and then you can add on from there. All right, Susan, let's just make sure I have it down so I can present in a coherent way. What were the data needs?

DR. TILTON: I had added that we were missing dermal absorption data. I also made a note that it would be helpful to have clarification regarding the percentage of the ingredients in the finished products.

DR. COHEN: Just point me to a specific location for that comment.

DR. ROSS: It's composition and impurities.

DR. TILTON: Yeah.

DR. SLAGA: Since the data on irritation was very mixed, we may want to address that with asking for more irritation data.

DR. COHEN: Yeah, that's on my list too. Okay.

DR. ROSS: David, I think you have to ask for the compounds at the highest purity possible. because That's one of the reasons we're getting variable data.

DR. COHEN: 30 to 60 percent of active agreements. So, how do we articulate that ask?

DR. ROSS: Very straightforwardly.

DR. BERGFELD: I think you can just ask.

DR. COHEN: No, what are we asking for?

DR. BERGFELD: You talking about irritation studies and what percentage you are asking, or?

DR. COHEN: Oh, no, no, no, no, no. That I -- so irritation and sensitization at max use, right?

DR. BERGFELD: Yep.

DR. COHEN: But the commentary on the purity.

DR. BERGFELD: You have to know the impurities then.

DR. ROSS: Well some of them you do.

DR. COHEN: We have them listed -- we have -- like amidoamine in there. The question is, are we going to comment about this issue?

DR. BERGFELD: We have to comment in the discussion about the nitrosation.

DR. COHEN: Okay, let's continue. Susan, so you want dermal absorption data. What else?

DR. TILTON: I don't know, I think David had a --

DR. COHEN: What else did you have, David?

DR. ROSS: I had the --

DR. TILTON: Sensitizing and max use.

DR. ROSS: I have DARTs. And again, as pointed out, more of that is coming. So, we know that's on the way but we don't have it right now. So, I felt we needed that at the highest purity possible. And then we needed an HRIPT with Sodium Lauroamphoacetate at max use, which is at 9.9 percent. Currently we have 0.5 percent.

DR. COHEN: Well we would take --

DR. COHEN: We would take it any of -- I mean if we're going to do some read across, right?

DR. ROSS: Well, that's the other point I was going to raise.

DR. COHEN: Right? I mean, well, I'll take max use of any of them at this point, at max use.

DR. BERGFELD: When you say highest purity, what are you talking about? Are you talking about the use?

DR. COHEN: That was the word I was trying to dig in on before.

DR. ROSS: Yeah. I was concerned that some of the issues we're seeing with variable data as related to the impurities. I don't know that for a fact.

DR. COHEN: You mean the irritation?

DR. BERGFELD: The DART you're seeing?

DR. COHEN: Or the DART?

DR. ROSS: Yeah. The DARTs. And Exponent, in their review, had a reasonable hypothesis. It didn't pan out to be correct, but they had a reasonable hypothesis that it was due to one of the impurities. That wasn't the case, actually. But, you know, given the numbers of impurities in these materials, it was a reasonable thing to consider.

DR. COHEN: What impurity would cause cardiac abnormality?

DR. ROSS: It was the EC- --

DR. COHEN: I don't remember.

DR. ROSS: Yeah, AEEA, in the Exponent report that they considered.

DR. COHEN: I guess the issue is, are the impurities present in the commercial product? And if they are, it's immaterial, it's a problem. Right?

DR. ROSS: They did some studies on the AEEA and it wasn't responsible for the cardiac malformations. At least it was higher dose than --

DR. COHEN: Okay.

DR. ROSS: At least that's my recollection of the conclusion of the Exponent report.

DR. COHEN: Okay.

DR. ROSS: And I'll just pull it up to make sure I'm quoting it correctly. Wave 2 --

DR. COHEN: All right, so I have dermal absorption data, DART, some of which is forthcoming. It's going to be hard to -- I don't know how to deal with that, specifically, except, you know, in the future we'll have that. And irritation and sensitization at max use. Anything else?

DR. BERGFELD: I know that we say that, but we accept anything.

DR. COHEN: I didn't specify which one.

DR. BERGFELD: Okay.

DR. COHEN: It's tricky when we have them all in the same report, right. We've never said that we need one of them at a very specific concentration, right?

DR. BERGFELD: I think we have.

MS. CHERIAN: We do.

DR. COHEN: We have?

MS. CHERIAN: Yeah.

DR. COHEN: So, then we'd want to use --

MS. CHERIAN: I think if we're missing a specific datapoint.

DR. ROSS: I think, you know, my read of the data here was we had HRIPT on the majority of the most frequently used compound and max concentration. I just have to read my notes here in terms of --

DR. COHEN: In the Wave 2 report?

DR. ROSS: Well, it came from the original review.

DR. COHEN: I got to go back to that.

DR. ROSS: So, Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate and Sodium Cocoamphopropionate. But, yeah, you've got sensitization there, I think, at max use. The only one that was missing for me was that Sodium Lauroamphoacetate.

DR. COHEN: What PDF are you on?

DR. ROSS: I'm on Page --

DR. TILTON: Page 19 of the Wave 2.

DR. COHEN: Page 19 of Wave 2.

DR. ROSS: Actually, I was deep in my notes, so I can't give you a PDF page.

DR. COHEN: These are clinical case reports and --

DR. TILTON: Or 18.

MS. CHERIAN: 17, I think.

DR. TILTON: Or 18.

DR. ROSS: So sensitization at max.

DR. COHEN: 10 percent.

DR. ROSS: Yeah, 10 percent on -- 5 percent on the propionate.

DR. COHEN: You know what, I read the other report, I think. Okay. Hold on a second.

DR. ROSS: I think the other report cleared those four compounds, the Sodium Lauroamphoacetate.

DR. BERGFELD: Right. A lot of stuff on that.

DR. COHEN: No, that would do it. So, should those be in the tables later on, on the dermal sensitization?

DR. ROSS: Yeah. That's all data, we don't usually put that in.

DR. HELDRETH: It can be. If the Panel is going to rely on the old data for their discussion, then we can bring it forward. Historically, we've not brought data from an old report in to it, unless the Panel relied on it for their current conclusion. So, if this is the data that will be relied on to clear sensitization and/or irritation then, yes, we can bring it forward in the other table.

DR. COHEN: Yeah, I guess I didn't take it as gospel until I got you guys to tell me that it was probably okay to use that. I'd be okay with that.

DR. HELDRETH: You know, the beauty of the Cocoamphoacetates is that as constituents, you have all the chain lengths between 8 and 18.

DR. COHEN: I thought Coco was 12 to, like, 16. You'll have lauros in there as well? Maybe not -- lauro's 12, right? Lauro is 12. But I thought Coco is like 12 to 16, not 8 all the way up.

DR. HELDRETH: I'll have to look at the table.

DR. ANSELL: That's what I remember as well. That lauro is a part of Coco, but --

DR. COHEN: Right lauro is the bottom of the coco and then it goes up to like 16. Maybe I've heard 18, but I thought it was like 16.

DR. HELDRETH: So, Table 3 on PDF page 36.

DR. COHEN: Are we on Wave 2 or wave --

DR. HELDRETH: In the report. So, it's in the draft report.

DR. COHEN: What, what --

DR. HELDRETH: PDF Page 36, Table 3.

DR. COHEN: Page 36.

DR. HELDRETH: You'll see the fatty chain lengths that come from cutting coconut -- or I should say -- not cutting it.

DR. COHEN: Chain length distribution.

DR. ANSELL: Coco is supposed to be out there?

MS. BURNETT: I don't know if it helps, but I have CAPB open and this is the fatty acid profile for CAPB.

DR. COHEN: Okay. Betaine is C8 to C18. That's a huge swath.

DR. ROSS: Big group.

DR. COHEN: It's very compelling. I'm okay with that. That really kind of swayed me.

DR. HELDRETH: Many of the single chain length names, when we're talking about cosmetic ingredients, they're derived from coconut. They take coconut and they cut out the chain lengths that they want. And so, not only is it the right length, it's probably from the same source.

DR. COHEN: And these are all saturated, right, and some of these are unsaturated, right?

DR. HELDRETH: Oleic and linoleic.

DR. COHEN: Are unsaturated, yeah.

DR. ROSS: And you know, David, we have an HRIPT for Disodium Cocoamphodiacetate.

DR. COHEN: What's that?

DR. ROSS: We have an HRIPT for Disodium Cocoamphodiacetate at 32 percent.

DR. COHEN: Where are you?

DR. ROSS: That's PDF of the reports. Page 29, right, at the top of Page 29. The end of that first paragraph on Page 29.

DR. COHEN: Yeah. Knowing that we can bring this in and it's okay. And we kind of know that the Cocamidopropyl betaine sensitization is probably coming from the amidoamine or dimethylaminopropylamine not the coca betaine itself. I'd be willing to just get rid of that need if we're going to bring this in. And then the question is, do we need the others?

DR. ROSS: Well, it's a first report I think -- well, let's not go that way. I think, yeah, you probably do need some of these requirements.

DR. COHEN: Okay, fine. So, our IDA is for dermal absorption and DART.

DR. BERGFELD: Are you going to add the caveat, and if positive, 28-day dermal?

DR. COHEN: For the dermal absorption data?

DR. BERGFELD: Yeah.

DR. COHEN: If positive. Okay. Yeah, but I think that's very compelling for the sensitization stuff.

DR. ROSS: The old data was quite strong.

DR. COHEN: And it clinically made sense to me.

DR. ROSS: And just when we -- as I said before, when we write this report, again, I don't know how easy this is to do, but if we can -- if we're bringing in read across sources, you know, I went deep into that ECHA document to figure out where this data was coming from. And then I got the Wave 2. And so, if we can identify in this new document where the read across data is coming from, that would really help me at least.

DR. HELDRETH: Do you mean within the ECHA data or do you mean just whether it came from ECHA or somewhere else?

DR. ROSS: If you've got a table which says, you know -- put a superscript there, read across from reaction product in the -- XXXX with Y. So then you know where that read across is coming from, if it is read across at all.

DR. HELDRETH: We have in the past, when there is a fair amount of read across in the report, actually created a read across table that shows, here's your read across sources and it would list the citations, where they came from and which ingredients are the read across targets in the report. And then list under there which tox endpoints.

DR. ROSS: That would help. Yeah. That would help.

DR. HELDRETH: Any directions that you can put in your Panel returns as to which ones are useful for which endpoints will help Priya a lot when she creates that table.

DR. ROSS: Yeah, I've got a few questions to it. And so, that's already in my returns, but I'm happy to help out afterwards.

DR. HELDRETH: Great.

DR. BERGFELD: Haven't we heard what you want, the DART?

DR. ROSS: Yeah. But even to clear the other data that comes in, where's the read across coming from?

DR. BERGFELD: Yeah.

DR. COHEN: Any other comments on this?

DR. BERGFELD: So you're going out for insufficient and your data needs, again, could be stated.

DR. COHEN: Dermal absorption data and if positive, further tox needs. DART, and that's it.

MS. CHERIAN: DART on a specific --

DR. BERGFELD: Okay. The amidoamine, you're putting into the discussion about nitrosation agents. The impurity, amidoamine?

DR. COHEN: In the discussion.

DR. BERGFELD: Yeah.

DR. TILTON: And then the next report will also include the Wave 2 information?

MS. CHERIAN: Yes.

DR. COHEN: Yes.

DR. TILTON: Okay.

DR. HELDRETH: So, you probably won't see this until December, so Priya has time to recuperate.

DR. COHEN: Yeah. That was a big load of info.

MS. CHERIAN: You wanted DART on a specific -- on Disodium Coco or just DART data?

DR. ROSS: The first one on the list where it was conflicting data.

MS. CHERIAN: So Disodium Coco at max concentration. Okay. And then Dr. Tilton mentioned clarification on percentage of ingredient in finished products. Do you want that as part of the IDA as well?

DR. COHEN: Can you repeat that for me?

MS. CHERIAN: Dr. Tilton mentioned it'd be helpful to have clarification on the percentage of ingredients in finished products. Do you want that to be part of the IDA?

DR. TILTON: And I think it was provided as a range, just a general range.

DR. COHEN: How do we word that insufficiency?

MS. CHERIAN: You would say percentage of ingredients as finished products in cosmetics. Because The ranges we have right now are just from TDSs or SDSs and we don't know what those ingredients are used in. So maybe specifically for cosmetics.

DR. COHEN: Wouldn't maximum concentration cover that or no?

MS. CHERIAN: We still wouldn't know the composition of the ingredient itself.

DR. BERGFELD: We never do. Formulations are not our format. We're just doing the ingredients.

DR. COHEN: That's what I'm trying to get my head around.

DR. BERGFELD: Well, you can also talk about the active concentration. If it's being broken down in any way, you'd want to know the active part of it. It's in the formulation.

DR. HELDRETH: So do you mean a concentration of components within one ingredient?

MS. CHERIAN: Right. Within the ingredient. Because this is a -- not of the product itself, but the ingredient within the product, the cosmetic ingredient. It's just an odd scenario because they're all solutions.

So, it could be labeled as Sodium Lauroamphoacetate, but the percent actives within Sodium Lauroamphoacetate kind of varies.

DR. COHEN: I see. And that, how does that influence our conclusion if we just really want to know what the maximum concentration in the final product is? So you're going in with 60 percent in the solution. Isn't that going to be adjusted for in the final concentration of the finished product?

DR. BERGFELD: It'll be diluted. And then you're going to have an active concentration. What the actual --

DR. COHEN: I'm good with the IDA ask, I just don't know how to articulate the IDA ask.

MS. CHERIAN: I understand.

DR. COHEN: Tell me if you guys have a verbiage for it. It's the concentration of the target chemical in the raw material -- in the --

DR. TILTON: Solution.

DR. HELDRETH: It's actually purity.

MS. CHERIAN: Right. It's purity.

DR. COHEN: It's purity?

DR. ANSELL: But isn't that how it's reported based on activity? I mean if it's 60 percent active and you --

MS. CHERIAN: Right. The problem is that we don't have that data for cosmetics ingredient itself, is what I'm saying. So I don't -- so the composition that I have, when it says the range of 30 to 60, I don't know if that's for cosmetic ingredients.

MR. BJERKE: That's how we handle it for Cocamidopropyl betaine.

DR. ANSELL: Yeah.

MR. BJERKE: Percent activity.

DR. ANSELL: Right.

MR. BJERKE: So, we had cosmetic grade, CAPB is supplied with 35 percent solids. CAPB activity is the percent solids minus percent sodium chloride. So then we had an example in baby shampoo. The formulation contains 13 percent CAPB raw material. CAPB activity of the raw material is 30 percent. So then the CAPB activity and the shampoo was 4 percent. So as long as we know what the activity is, then we can dial down to what the actual exposure is. So I think activity is the appropriate way to ask the question.

DR. BERGFELD: So active concentration?

MR. BJERKE: That's right.

DR. BERGFELD: Active concentration you're asking for.

MR. BJERKE: Or percent activity in --

DR. COHEN: Active concentration in cosmetic grade material?

DR. BERGFELD: Well, I don't know if you can say cosmetic grade.

DR. COHEN: No?

DR. ANSELL: No, it's not the material, it's the tested formulation. Right? Is that --

DR. COHEN: Boy, I'm all tied up here.

MS. CHERIAN: These ingredients -- products. Christina, do you remember how we asked for that specific data in CAPB?

MS. BURNETT: No, I'm looking at the report right now. I'm trying to see where it's --

MS. CHERIAN: Because we asked for the same thing for CAPB.

MS. BURNETT: Yeah. I'll have to think and see if I have it written somewhere.

DR. ROSS: I mean, aren't we just asking for more information on composition? More specific information on composition and impurities where available? Because that's what we're trying to get at. What are the impurities and what the percentages are. We've got some information here. Is there other stuff out there that we're not aware of?

DR. COHEN: So Table 4 has composition of a number of these. I guess for Disodium Lauroamphodiacetate it's 30 to 60 percent. And then we're missing 40 to 70 percent of what else is in there?

DR. ROSS: Well, it's water of salt acids.

DR. COHEN: But it doesn't say it for that one. It doesn't say it for Lauroamphodiacetate.

DR. ROSS: Yeah. And I just didn't want to be surprised by other impurities that we're not aware of.

DR. COHEN: So, Cocoamidopropyl betaine is supplied as a solution in water and with sodium chloride, the concentration of CAPB and such applied materials is described in its activity. Concentration of cosmetic grade is what is left in the supplied solution after water and sodium chloride have been accounted for.

DR. BERGFELD: That's what Don said.

DR. COHEN: Which is 30 percent of the supplied solution. Yeah.

DR. BERGFELD: What is that?

DR. HELDRETH: So, further composition and impurities data?

DR. COHEN: Yes. We definitely need to land this plane because we're running out of gas.

DR. BERGFELD: And active concentration. Put the word active in there. Let us know what is real, what it is.

DR. COHEN: Further information --

DR. BERGFELD: Can't do the arithmetic.

DR. COHEN: -- regarding what?

DR. ROSS: Composition and impurities of cosmetic grade ingredients.

DR. BERGFELD: I don't know if you can say cosmetic.

DR. COHEN: They do say it here.

DR. HELDRETH: They do.

MS. BURNETT: They use it in CAPB. It's says cosmetic grade.

MR. BJERKE: It's not a regulatory term, I think it's a supplier term.

DR. BERGFELD: Okay. And they supply other reasons too -- so it's just the name they put on it for you. Let's take it off.

DR. COHEN: Okay.

DR. SLAGA: The audio has gone extremely bad with you all.

DR. COHEN: You should thank us for that, Tom. But is that better.

DR. SLAGA: I can understand you, but several of the other people I can't.

DR. COHEN: So, we'll bring our mics in a little closer.

DR. SLAGA: You either have to be closer to the microphone or something.

DR. COHEN: Okay.

DR. SLAGA: Can you hear me now?

DR. COHEN: We can hear you beautifully. Okay, I think we got it.

DR. BERGFELD: I think we do.

DR. COHEN: Yeah.

DR. BERGFELD: I think active concentration, though, active. And I really do think, if Don is correct, that the supplier supplies it to all kinds of people and they just put the cosmetic on the one they're sending to us. It may not be any different. I don't think we should put cosmetic on it.

DR. ROSS: Okay, that's fine.

DR. COHEN: And the reason for pulling that out is why?

DR. BERGFELD: It infers that it's really a cleaned up ingredient.

DR. COHEN: And is it --

DR. BERGFELD: It may not be.

DR. ANSELL: There are trade names that we sell. But there's no cosmetic specifications.

DR. COHEN: Yeah, I got it. Like sushi grade tuna.

DR. ANSELL: Right.

MR. BJERKE: Yeah, one additional comment about the CAPB, is when we talked about the sensitizing impurities, DMAPA and amidoamine, at one point we discussed whether we want to control those impurities to a level that would cover everything. And we changed the approach to basically say, those impurities should be supported by a quantitative risk assessment for contact dermatitis.

For example, you could have higher levels of an impurity, like amidoamine in a rinse off product, and still not have a sensitization concern. But if you have higher exposure in a leave-on product, you may need a higher quality of CAPB with lower amidoamine concentrations.

DR. COHEN: Yeah, very logical. Okay.

MR. BJERKE: So, I think reporting what those impurities are and the levels are important. But then handle whether they're safe or not, based on a QRA for the particular cosmetic product used, and the level of that impurity in that raw material.

DR. COHEN: I find that very satisfying. Yeah. Okay. Can we close Amphocarboxylates?

DR. BERGFELD: Absolutely.

DR. ROSS: Please.

DR. COHEN: Move onto something simple like yeast. All right.

Full Panel – June 13, 2023

DR. BELSITO: The name has been changed from Amphocarbomates to carboxylates, to include the propionate salts. We got a huge data dump in Wave 2. We're not clear whether some of that data is duplicative from data that was in the original report. Overall, we think that these are likely safe as used when formulated to be nonirritating. But we would like to table this to have the report reorganized in a uniform report.

DR. COHEN: We'll second that.

DR. BERGFELD: And that is residing on the fact that the data dump disallow for full evaluation, or timely evaluation?

DR. BELSITO: No, I think it allow for full evaluation. It's just that our team would like to see the report fully organized. Some of the team members had already reviewed the original, and didn't really have time to go through all of the data on this. So, just to give everyone time to review what was in the Wave 2.

DR. BERGFELD: It's been agreed to table. And table has no further discussion. I'll just call for the vote on tabling. All those agreed to table? Thank you. I think it's unanimous.

DR. HELDRETH: Yes, I think it's unanimous. And maybe also since so many of you went through and looked at the data that was available, if there are any known data gaps at this point, we can include that in our post-meeting announcements so that suppliers can help fill that in in the meantime.

DR. BELSITO: I went through it all. I think that when we look at it the data will be sufficient formulate to be nonirritating.

DR. COHEN: Can we go through our list with you and just, I mean, help us out.

DR. BELSITO: Sure.

DR. COHEN: We were asking for absorption data. DART, we understood some additional DART was forthcoming, particularly with the cardiac malformations for the Disodium Cocoamphoacetate.

DR. BELSITO: All of that DART information, when you look at Wave 2, was reviewed by Expedient --

DR. ROSS: Exponent.

DR. BELSITO: And, you know, it was thought that that one DART study with the cardiac effects was spurious.

DR. ROSS: There's no dose response, I would agree with that.

DR. BELSITO: No dose response.

DR. ROSS: I wouldn't necessarily agree it was spurious. It was -- you know, another study it was clean. That one was flagged. And then in the Exponent report, there was actually another reference which had a very low incidence of cardia malformations. And I gave that yesterday, I think you have that reference. And so, I felt we should have a full discussion of that.

If more DART is coming, I think that it would be prudent to look at that given those two studies. I mean, okay, one has no dose response, one has low incidences, but I think it would still be prudent to look at the additional studies if or when they arrive.

DR. BELSITO: Those aren't going to happen for another two years.

DR. ROSS: Well, I think there was one, April 24th, so it's still quite a ways out.

DR. BELSITO: Right. And the other is like late 2025.

DR. ROSS: That's 2025, yeah. But there is another one coming. I don't know what speed it'll come.

DR. SNYDER: Again, those studies were at very high doses, 300 mg/kg was the lowest dose. I mean, that's way above cosmetics. And I thought that Exponent, they did a nice job of summarizing better than I could've done spending weeks looking at the data. No individual study had a specific significance. They even combined all three studies and still didn't flag, so --

DR. ROSS: And the key is it was no dose response.

DR. COHEN: Wasn't the control negative?

DR. ROSS: Control was negative.

DR. COHEN: Control was negative.

DR. ROSS: But there was no increase as you went up in dose. But I still think at least we wanted some more clarification about that.

DR. BERGFELD: David, do you have any other needs so they can record those?

DR. COHEN: Yes, some further information regarding the composition and impurities of the cosmetic grade materials, sort of in the way that it showed up in the report for Cocamidopropyl betaine. It's a big range. And the description of what is active material and not active material was a bit complicated.

DR. BERGFELD: Yeah, go ahead if you have more.

DR. COHEN: No, I think we got everything, and maybe an organization of this irritation and sensitization, we'll review it. Do you think we have sensitization at max use, which is 9.9 percent for Sodium Lauroamphoacetate? We had that as a data need.

DR. BELSITO: I didn't flag it, so --

DR. COHEN: We'll go back to it when we see the report.

DR. BELSITO: I mean, again --

DR. BERGFELD: Well, we have all of these listed and we'll see those hopefully in the summary that precedes the new document, so that we can make sure that we have checked off all of our boxes.

I think this brings to light the fact that a large data dump two days before coming is a problem. And I want to say that we've developed a process now to table until we can fully examine materials we get comfortably. So we just put that on record, all right?

DR. COHEN: So this will be a table with additional commentary about our needs.

DR. BERGFELD: Yes.

MS. CHERIAN: I had a question about the read-across ingredients, those three extracts. Which ones do we want to see data on and which ones we don't want to see it on? I'm talking about the C08-18 or the C12, I'm talking about those three additional ingredients that were listed in the Wave 2 memo.

DR. ROSS: The Betaine, the imidazole and the beta-Alanine, right?

MS. CHERIAN: Yes.

DR. BELSITO: We discussed that, did not feel that we could use them as read-across. The Wave 2 memo. Let me go that.

DR. COHEN: Susan, you mentioned the Betaine you couldn't use for dermal absorption and tox, right?

DR. ROSS: I think we thought the additional two were okay. Allan, what was your thoughts about that?

DR. RETTIE: Yes, my notes say the Betaine, of course, no. The other two, I felt that the composition data was still vague, especially when you compared it with the very detailed explanations of what a given fraction contained from the European data.

In our data tables here, it gives the impression that each of these are pure compounds for some of them. Yet, we use the same synthetic approach to make these. And the European documents stress that these mixtures, beyond the fact that they were monoesters and di-esters, also might have ethers in them.

And so, I just felt that until we got clarification of the composition of what the ingredients we're looking at, in terms of their complexities, it was just very difficult for me to draw any conclusions about those. So, I would just reiterate that, at least from my end, I'd like to see much clearer composition data in our report. We need that so that we can evaluate read-across.

I think that number two here could be fine. But it specifies unsaturated fatty acid chains. We don't know whether we got those. I think that read-across is probably okay, but I would like to know what the composition, saturated versus unsaturated, for the fatty acid chains is in our ingredients before I would --

DR. COHEN: That was part of our ask.

DR. BERGFELD: So, that's another need that has to be clarified? Okay.

DR. ROSS: Yeah, I mean, these things are written up as UVCB, unknown variable composition biomaterials, which was probably some of the reason for the conflicting data in this report. But I think your call for more information on composition is a good one. We felt what we had, we could probably, looking at the reaction mechanism, go with read-across for the imidazole and the beta-Alanine compound, but we're certainly willing to wait until we have more composition data. I think that's a really good strategy.

DR. RETTIE: I agree with the read-across for the Beta-Alanine. I mean, it's a direct analog, It's just a shorter chain length. It's a heptane analog.

DR. BERGFELD: All right. It sounds like we have a plan here. And this particular ingredient has been tabled with all these needs being reiterated. So we're going to move on to MIBK, Dr. Cohen.

JUNE 2024 PANEL MEETING – SECOND REVIEW/REVISED DRAFT REPORT

Belsito Team – June 3, 2024

DR. BELSITO: Then we're moving on to the fatty amphocarboxylates. So, again, before we start that report, Allan, do you want to update us on the Read-Across Working Group?

DR. RETTIE: Sure. So, going back to the general summary comments that I read earlier, we had all the issues we've been talking about with regard to very potent receptor-based interactions. Now, these don't apply here, but what does apply is read-across when mixtures may be involved. Clarification of the composition of the -- is it 11 ingredients that we have here? -- 11, I think, is something we'll get to.

So, this is where the betaine example, which I tried to bring up earlier and shouldn't have done, applies. Much of the arguments seemed, to me at least, to rely on read-across from the betaine. As I mentioned earlier, the group, all of us, even before we had the Read-Across Working Group together, did not accept the notion that using the permanently quaternary ammonium charged compound was appropriate.

DR. EISENMANN: I thought they're only proposing that compound for dermal penetration, period, is my understanding. And, to me, it's just getting them into the ballpark.

DR. RETTIE: Okay. Well, we'll take that under consideration. I think you're right. But while I'm still on the betaines, an argument made for potential read-across to the amphocarboxylates for dermal penetration for both surfactant groups are ionized at all pHs, and we acknowledge that that's true. But it's a different circumstance when we move away from the betaines. Amphocarboxylates do not have a charge nitrogen under alkaline conditions, and they're uncharged, of course, at the isoelectric point or largely uncharged in the isoelectric range. We considered that these distinctive features might affect tissue distribution. So, we started in with that because we had begun with discussion of the betaines before, and alkyl betaines have been through this group and reviewed positively in the past. What else do we have here?

Once again, we came to the tentative conclusion that read-across for highly-sensitive toxic endpoints are not appropriate. And in this case here, we have concerning tox signals such as cardiac abnormalities, just another complicating feature. We were worried about that especially since we have no mechanistic underpinning for that observation.

DR. BELSITO: So, the Exponent analysis of that DART and -- we have one study of several.

DR. RETTIE: Did we disregard it because it was --

DR. BELSITO: Yeah.

DR. RETTIE: I had the impression there were three separate studies that brought up the same cardiac malformation.

DR. BELSITO: Think it was only one, no?

DR. RETTIE: Paul, did you get into that, the number of studies that brought up cardiac malformations?

DR. SNYDER: I did not. I did not.

DR. BELSITO: Well, Table 8 summarizes all the repro studies we saw. So, if we look at Table 8. Okay. Gavage. No treatment-related effects. Another gavage. No external or visceral malformations. OECD TG 414 was again a gavage. No adverse effects related to developmental parameters were observed in the fetus. So --

DR. SNYDER: In that study, it was positive. They couldn't determine an NOAEL for that effect either.

DR. BELSITO: Right. There was no dose response, right?

DR. KLAASSEN: That's what they said.

DR. BELSITO: So, we have studies with NOAELs above a gram per kilogram. Gavage studies, by the way, which people criticize for overwhelming defense systems.

DR. RETTIE: So, are we centering around that single cardiac abnormality study here then?

DR. EISENMANN: I thought that John DeSesso's report that was provided at the last meeting was useful in that he took all the studies together and combined them.

DR. BELSITO: Right. That's the Exponent report.

DR. EISENMANN: Right.

DR. BELSITO: Yeah. I mean, I found that very helpful as well, and we've agreed to take in outside expert opinion on an ad hoc basis. I think this is one opinion we should take in. And I'm not really concerned about the DART effect. I mean, I think that it is spurious. There was no dose response, and it's inconsistent with everything else we have, the gavage studies we have, wasn't seen. But it's not my area of expertise, so I'll see to other people.

Paul, I usually go to you for repro. What did you think?

DR. SNYDER: Yeah. I mean, I thought in June of 2023 we asked for more DART, and we have not received any more data since then, right. So, are we saying we're not concerned anymore about DART, my notes say?

DR. BELSITO: Well, I think we asked for it because David Ross wanted it, not because we wanted it.

DR. SNYDER: Okay. All right.

DR. BELSITO: If you go back with the original, I think we're willing to start with safe as used for this group.

DR. RETTIE: Yeah, I know from what I recall, the reading work across group, Dave is the main proponent for additional DART studies for that. Not my area of expertise either.

DR. EISENMANN: In their update, they've said there's a rabbit study underway, and there's a one-gen underway for ECHA. But the one-gen's going to take a while for it to be completed.

DR. RETTIE: So, to consider additional DART data, we're likely looking at a long time.

MS. CHERIAN: September-October.

DR. RETTIE: Oh, that soon?

DR. EISENMANN: That's when they give a report. So, however long it'll take them to finalize a report after they get it, so it might be a while yet.

DR. KLAASSEN: Yeah, they say that there's no dose response, and we have to kind of take their word for it. What might be interesting is that if we can get the number 24 report, which this comes from, what does the actual data look like? Instead of concluding there's no dose response --

DR. EISENMANN: Some of the actual data is in the Exponent report.

DR. KLAASSEN: That's in the Exponent report?

DR. BELSITO: Yeah.

DR. KLAASSEN: Okay.

DR. BELSITO: Reference 24 is the Exponent report.

DR. KLAASSEN: Oh, that is it.

DR. BELSITO: Yeah. DeSesso is the Exponent report looking at all the data.

DR. KLAASSEN: Okay. We had that the last time but not this time.

DR. SNYDER: (Inaudible) data to clear all the other IDAs, the dermal absorption, composition, impurity, sensitization?

DR. BELSITO: Not sure of your question. Did he clear read-across for those, or what was your question?

DR. SNYDER: No, before, we came out with an insufficient data announcement for four items in addition to the DART. So, I just wanted to be clear. Did we get data, because my notes say we received no new data?

DR. RETTIE: I mean, that report went into some detail about the AEEA effects or lack thereof, and they excluded the AEEA as being a contributor to the toxicity observed. But that leaves us with no working hypothesis or any kind of clues about what might underlie this serious toxicity. And so, if we can get anymore clarification on that, I think the Working Group would appreciate it.

DR. KLAASSEN: Monice or Bart, could you send me that DeSesso review that we saw the last time. I could read it tonight again. I know we talked about it three months. It looked pretty good then, but I'd like to read it again.

DR. RETTIE: Could you CC me too, Monice? Save me digging out.

DR. BELSITO: Just send it to everyone.

DR. KLAASSEN: If I recall right, the quality of the products in this class were not great. Am I remembering correctly?

DR. BELSITO: Well, none of them are pure. They all have active ingredient probably as much as 50 percent if you're lucky, and then they have other material. But the other material is reportedly things like water and other inactive, quote-unquote, for lack of a better word. You see that -- it's in Table 1 or 2.

DR. KLAASSEN: I remember.

DR. RETTIE: It's in Table 4, composition of tradename mixtures. We have compositions for -- one, two, three, four, five -- five of them. And as you said, large component of the preps, as listed here, are water, up to 70 percent. What's not listed here but which I wondered about at least having a declaration that when we were talking about an acetate we did not have the diacetate, when we were talking about a propionate, a declaration that we don't have the dipropionate because this mono-, di- piece is missing from here. And from what I read of documents that came from Europe, it was common that mixtures of the mono- and di- constituents were being used. I felt that was a little problematic and made it a little difficult for the Read-Across Group to know how to deal with that.

I kind of feel that monoacetate to monopropionate -- this is just me -- is probably okay. I have more concern about monoacetate to diacetate, monopropionate to dipropionate just because you got a bigger molecular weight. It's farther away. Maybe it's okay to accept it as read-across, but I just didn't know what we were dealing with composition-wise in the current report.

DR. BELSITO: Why would the greater molecular weight bother you?

DR. RETTIE: Well, again, it's read-across, and mostly when you're thinking about read-across and applying simple rules, you want to go as close as you can to the chemical structure. And so, it's less of a distance from the monopropionate to the monoacetate, as compared from the monoacetate to the diacetate or the dipropionate here.

DR. BELSITO: But we're also looking at something that first has to be dermally absorbed.

DR. RETTIE: Yep.

DR. BELSITO: And would you expect a diacetate to be more or less absorbed than a monoacetate?

DR. RETTIE: I felt it should have a higher log P, and I thought it should be probably more absorbed than less absorbed. The log Ps that were reported in the document here weren't that clear to me. The ranges that we're reporting make an awful lot of sense. Now, the log Ps in our tables here for chemical properties, Table 2, go from minus-8 all the way up to 0.5. Seems very wide, so I was just questioning what the compositions were.

DR. KLAASSEN: I thought if there was one thing that in silico could do for us was to give us the pKa in these physical properties, and apparently, it can't even do that.

DR. RETTIE: Well, it might because I have a note here that we're using three different programs to estimate.

DR. KLAASSEN: Yeah, I know. Maybe I was naïve --

DR. RETTIE: No, no.

DR. KLAASSEN: -- because I thought, man. I took those numbers as rock solid until I saw this. And being so different, I don't know what to believe anymore from in silico.

DR. RETTIE: I mean, it gives us some information about the range of log Ps that you'd estimate for really the part of the molecule I wasn't that concerned about, which was the acyl side chain variation all the way from C8 up to C18. I would've like to have seen information on the log Ps, which should be easy to get, as you say, for the monoacetates and diacetates, but maybe I'm completely wrong here and the composition of these compounds that we're looking is absolutely as described. But like I said, it's quite a bit different from what I was reading in the ECHA documents, so I was just suspicious.

DR. EISENMANN: The wheatgerm one came from a NICNAS document, was not estimated by us. I wonder if it would be good if you guys did an estimate. I think they picked a specific structure that's predominantly in the wheatgerm oil. I don't remember what fatty acid they picked. That's the real outlier, that 0.5 percent.

DR. RETTIE: Zero-point-five. Yeah, that's right.

DR. EISENMANN: Oh-point-five (inaudible) percent. So, it might be good if you guys did the -- I don't know if you did the calculations for the other ones or not, or if they came from references. But that one might be good for you guys to do an estimate.

DR. HELDRETH: Yeah, we just used EPA's EPI Suite and just plugged in the SMILES codes for the two ends of the possible chain links. Since we're talking about coco-derived C8 up to C18, we get both of those ends of the range.

DR. EISENMANN: So, to be consistent, put in the wheatgerm just out of curiosity because that came from a different source.

DR. HELDRETH: Okay.

DR. RETTIE: Thanks. I would just like to reiterate that my concerns fall out if we accept the purities of the mono- versus diacetates as stated here. But just would like somebody to tell me why they're so different from the ECHA compositions. Seems like a disconnect. Are these call them purified, HPLC-purified, in the U.S.?

DR. EISENMANN: I don't know. I have to look back and see where that data is coming from. But the people that are providing data is the ECHA Consortium. They're the ones that have the data ongoing.

DR. RETTIE: Okay.

DR. EISENMANN: I mean, they're testing their mixtures, I think.

DR. RETTIE: And in that document somewhere, there's up to 25 percent of the diacetate in one of these, or more, because it's here. That was my concern. Why don't we see 25 percent of the diacetate? I mean, it should be fairly innocuous. I don't want to make a big deal about it. It's just the lack of consistency between the ECHA document and what we're looking at in Table 2, I guess -- no, Table 1.

DR. HELDRETH: Yeah. So, in Table 1, we presented exactly what you would find in the dictionary monographs. But document folks that actually make these sorts of materials where it's like they took coconut acid. They took a cut of coconut acid, has a range of like C8 to C18. And then they're reacting it to make the amphoacetate or to make it diacetate.

DR. RETTIE: Sure, I understand.

DR. HELDRETH: And even though you might call it disodium cocoamphodiacetate, both the ingredient itself and any source materials that we were reading from, they're probably all mixtures of monoacetates and diacetates to some extent but with a peak that's higher, for example, the diacetate when it's named diacetate, and a peak that's higher for the monopropionate when it's named monopropionate. But I think it's always a mixture. And you see the same kinds of mixtures from the source materials and the ingredient.

DR. RETTIE: So, you'd say that it's always a mixture, not only at the level of the acyl side chains, which we kind of all understand, but given the synthetic methodology making the imidazoline and then opening it up, it's always a mixture of the monoacetate or the diacetate.

DR. HELDRETH: That's my understanding of it. Sitting and talking with the folks on the INCI Committee who actually have experience making these sorts of things, you take even a mixture of the fatty acid side chains and try to do acetylation of that, you're going to get mixtures because you're starting with mixtures, and it's just a challenge. You can push the majority to be one or the other, but to get exclusive and then to do separations on it -- I mean, you can do separations like that in a lab, but on the large scale, probably not worth the effort. And why? What are you excluding in a --

DR. RETTIE: So, the level of the Read-Across Working Group's deliberations about this one, we were kind of stymied because I don't know that we had that amount of clarity at the Read-Across Working Group. And so, we honed in on the idea that, when you've got mixtures in your ingredient, mixtures of these analogues basically, we weren't really sure how to deal with that. So, we stopped short.

My feeling is the read-across to the diacetates -- the diacetates are going to have bigger differences I think in terms of physical chemical properties. But maybe it's all awash if they're all a mixture of monoacetates and diacetates or monopropionates and dipropionates. Certainly something we should talk about again in the Read-Across Group.

DR. BELSITO: Does the method of manufacturer on PDF 41 that's given for these help you understand in any way the fact that they would like -- I mean, I'm assuming that this is a generic method of manufacture for both the mono- and the diacetates, is that correct?

MS. CHERIAN: First paragraph?

DR. BELSITO: Pardon?

MS. CHERIAN: The first paragraph?

DR. BELSITO: Yeah.

MS. CHERIAN: Yes.

DR. RETTIE: So, we're on PDF 41, first paragraph, Method of Manufacture?

DR. BELSITO: Yeah.

DR. RETTIE: Yeah. So, as I mentioned earlier, yeah, it tells us we get a substitute, imidazoline, which then gets reacted and splits. As I understand it, it's the same method of manufacture as is outlined in a figure in the ECHA documents, and it shows both monoacetates and diacetates being made from the same method of manufacture, which is where I started with this and wondered why we didn't have the di-, just had the mono-. But based on Bart's comments, I can understand that a little bit better now. I'm just wondering if we have more detailed information for the tradename mixes. Do they give more detail, and is that what we should be including?

DR. HELDRETH: My understanding with the tradename mixtures is these aren't the ingredients themselves that we're talking about purity. These are essentially like pre-formulations. So, it's the ingredient plus this and this and this, so that when someone at a finishing house includes one of these ingredients, it meshes well with the rest of the formulation.

DR. RETTIE: But it therefore doesn't shed any light on whether it's 15 percent of the dye or 25 percent of the dye.

DR. HELDRETH: Right. Right.

DR. RETTIE: That's just an unknown, and we can't get that info, it sounds like. Well, it may simplify read-across if we can, as the Read-Across Working Group, accept the fact that the mixtures are going to be heterogenous, as we're discussing here. And it's not a huge jump from the diacetate from the monoacetate. It's further than I would like, but can I say it precludes read-across? Maybe not. I'd like to have a chat with the rest for the members of the Working Group to decide that.

What do you think, Curt? Do you have strong feelings?

DR. KLAASSEN: I have no strong feelings.

DR. BELSITO: Paul?

DR. SNYDER: No. That chemistry's a little bit not in my (inaudible). One of my concerns too, Don, is that -- not to change the subject or anything -- but we now that we know there's a rabbit repro study and a one-generation repro study that's forthcoming, are we going to wait until we see that data? Or are going to go ahead and -- because this is a, yeah, draft report. So, maybe it'll be done by the time we get to final.

DR. BELSITO: Yeah, I mean, that was one of my comments in a note from on the developmental and repro tox study. Do we want a table for the data promised on those studies and also for final decision on read-across?

DR. HELDRETH: Yeah, you could either go that way or, since it wouldn't come back till this December panel meeting at the soonest anyway, you could just put out an insufficient data announcement that includes those pieces. Either way will work. It's the Panel's prerogative.

DR. BELSITO: I mean, again, the one positive DART study, there was no dose response. We have an LLNA which is negative at 30 percent, negative guinea pig maximization test. I mean, I really thought that we could go with safe as used when formulated to be nonirritant. And if you were concerned about the amidoamine impurities, deal with it the same we deal with the betaines and say formulate to be non-sensitizing. But I guess we want to await the further DART studies and decisions from the Read-Across Working Group. Is that what I'm hearing from my team?

DR. SNYDER: Yeah, I was getting the same message from Allan there regarding the research -- or the Read-Across Working Group. I mean, I still think they haven't kind of got their guidance for how they're going to approach these things. So, in addition to that, I mean, why would somebody be doing a rabbit repro study and a one-generation study if everything was this clean as we're saying? So, I don't quite understand the basis for that.

DR. EISENMANN: Because ECHA is making them do it based on volume of use. They had a response in their comments on why they're being made to do it. It wasn't a concern; it was just because of the volume.

DR. SNYDER: All right. So, they're just checking a box. Okay, thank you, Carol, for that clarification.

DR. KLAASSEN: I guess, it seemed --

DR. SNYDER: So, if Allan's okay with the read-across, Don, I'm okay with what you propose. We can put it back out there as a safe as used when formulated to be nonirritating and let the other group drive the discussion.

DR. BELSITO: Well, Cohen is actually -- their team is starting the discussion.

DR. RETTIE: Perhaps the last point of clarification from the Wave 2 the first time around, there was some confusion about what amidoamine was. Do we still care about that? You asked me a question, and I didn't know the answer. But turns out that both of the compounds that were being described, amidopropyl dimethylamine and this dodecyl compound -- well, they're both amidoamines, but one's a C16. One's a C12. I don't know that we need to keep going on this, but I just wondered if it was still an outstanding question for the group.

DR. BELSITO: The amidoamine becomes an issue if it's a residual -- the starting material is a residual and what's marketed because it's a sensitizer. So, we had this issue with a group of compounds called betaines that we reviewed before you joined the Panel where there were questions about sensitization to betaines and whether they were due to dimethylaminopropylamine or to amidoamine. We went back and forth, and there were some positive sensitization data, negative sensitization data. Anyway, the long and short of it was that it was resolved by saying that they were safe as used when formulated to be non-sensitizing based upon a QRA or other similar methodologies. Which we could do here as well if we were concerned about potential sensitizing starting materials that remained in the final product.

So, to answer your question, Allan, no, it doesn't matter whether it's C12 or C16.

DR. RETTIE: They're both known sensitizers. Okay.

DR. BELSITO: I had a question for you, Carol. When we're getting these concentrations of use, are we getting the concentration of the mixture, or we're getting the concentration of the, quote-unquote, active ingredient, the amphoacetate that we're looking at in the final product?

DR. EISENMANN: (Inaudible) I'm asking (inaudible) concentration of the active.

DR. BELSITO: You're asking.

DR. EISENMANN: Yeah.

DR. HELDRETH: Good answer.

DR. EISENMANN: So, that's what I want them to give me. I don't have access to their files, so that's what I'm asking them.

DR. BELSITO: So, we have to operate under the assumption that they have told you the concentration of the active.

DR. EISENMANN: And I do my best if something seems out of place to go back and say, is this real? Or is this correct? Though, sometimes, if I do right away, the person -- they just looked at it, so they assume that it's correct. But if I go back a few months later, somebody else might be looking at their database, and I sometimes get a different answer. But, yeah, it is (inaudible). They change their formulations too a fair amount, so it is moving. Concentrations of use are moving targets, I've decided.

DR. HELDRETH: Part of the reason we have the caveat as described in this report.

DR. BELSITO: Right. Okay.

DR. KLAASSEN: The name can stay the same, but the ingredients can change. The first time I came across this was with Tide soap. Tide soap used to have a lot of phosphate in it, and then they got all this fungal growth and what have you in the rivers and stuff. So, they took it completely out and reformulated about 98 percent, and it was still called Tide. Is that right?

UNIDENTIFIED MALE: Yeah.

DR. KLAASSEN: So, the name can stay the same, but the ingredients can change.

DR. BELSITO: Okay. And just Allan and Curt, since you're in the Read-Across Working Group, the lamidopropylbetaine is being asked for a read-across for absorption only, not for other endpoints, if you remain concerned about absorption. So, it's --

DR. RETTIE: Yeah. And I felt the C12 was the most prominent constituent, so probably is the best candidate for selection there.

DR. KLAASSEN: I'm okay with that.

DR. BELSITO: Okay. So, just going through the documents. I mean, I know we're going to table this, but again for -- Priya, this is your document as well? Boy, you're a lucky lady, aren't you?

MS. CHERIAN: I know.

DR. HELDRETH: She gets all the fun ones.

DR. BELSITO: Yeah. Okay. I don't have any additional -- oh.

On table -- well, PDF Page 65, it's Table 10. For the LLNA on the top one, the sodium lauroamphoacetate, we described the ear thickness increases. You didn't give values for the stimulation indexes because the ear swelling could simply be secondary to the irritation that we know these have. So, it would be helpful, at least for me, in terms of sensitization if you put the SIs for the different concentrations for the EC3s, if they were given.

Okay. Then we had a Wave 2 on this. Let's just discuss. We received comments from the Council, which I thought were all fine. Curt, Allan, Paul, did you have any?

DR. RETTIE: I did not.

DR. SNYDER: I did not either.

DR. BELSITO: Okay. And then we received comments from the REACH Amphoacetate's Consortium asking us to, again, look at the Exponent analysis. But since they're already doing a rabbit study and other DART studies, my hearing from you all is that we're going to table this and wait for those DART studies before reopening it again or looking at it again.

DR. SNYDER: No, I probably retracked that based on Carol because, if it's just to meet data needs based on volume of product, not based on any concern. I think there's certainly sufficient studies that are under that table. So, I would be okay with going back to the safe as used when formulated to be non-sensitizing.

DR. BELSITO: And non-irritating.

DR. SNYDER: And non-irritating. Sorry, yes.

DR. BELSITO: Okay. So, now we're coming full circle. We don't need read-across. So --

DR. SNYDER: But that's based on if Allan's okay with that.

DR. BELSITO: Pardon?

DR. SNYDER: Pending Allan's input on that.

DR. BELSITO: Well, Allan's input on what, read-across? Because if we're going safe as used, what we're saying is we don't need additional read-across data at this point, right?

DR. SNYDER: Yes.

DR. KLAASSEN: By definition.

DR. BELSITO: Right. So, Curt and Allan, what do you think of that approach, which was our initial recommendation? I mean, these data needs all came from the Cohen team, not from our team.

DR. RETTIE: Again, I feel a little naked talking about the Read-Across Working Group without the other members.

DR. BELSITO: We're not talking about reading. We're talking about not having read-across at all based upon the information that you're seeing in this document. And Wave 2, do you feel they're sufficient, or do you feel that we still need read-across? And for what endpoints, do we need read-across for?

DR. KLAASSEN: I think it's sufficient if I can read this document tonight, that Exponent sent, and to make sure I remember that correctly. And if I do, I think we can go as Paul said.

DR. BELSITO: Sufficient when formulated to be non-irritating, and we can talk about the sensitizing endpoint that whether it's non-sensitizing or not. I don't think we need it for this one. I'm not that concerned about the level of residual amidoamines. But I don't think the other team is going to go safe as used, by the way, but that doesn't matter. Allan, your thoughts?

DR. RETTIE: I can go along with it.

DR. BELSITO: Okay.

DR. RETTIE: We don't need for read-across.

DR. BELSITO: So, Curt, you're going to give me a heads up at some point before the meeting?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay.

DR. KLAASSEN: As long as someone sends that article to me.

MS. FIUME: It should be in your inbox.

DR. KLAASSEN: Okay, great.

DR. BELSITO: Okay. Is there anything else? Wave 2 was the fall of the various, looking at the in silico predictions for potential read-acrosses. So, I think we've covered the comments in Wave 2. Okay. Anything else on the amphoacetates?

Priya, have we completely confused you as to where we are?

MS. CHERIAN: I'm okay right now.

DR. BELSITO: Ask you again tomorrow morning?

MS. CHERIAN: Yes.

DR. BELSITO: Okay.

Cohen Team – June 3, 2024

DR. COHEN: Okay. We're going to move on to fatty amphocarboxylates. It's like we're doing a lot of the heavy lifting early today. So, this is a revised draft safety report for fatty amphocarboxylates who was first reviewed in June of 2023 at which time the panel tabled the review due to receipt of a large amount of information in Wave 2. It included various fatty chain mixtures that are listed and reach dossiers for the following substances that are listed here as well.

The CIR prepared a read across justification table and the Read Across Working Group met to adjudicate that. Also, in June, the panel noted that the following data points were needed. Dermal absorption/DART on disodium cocoamphodiacetate and further information regarding composition and impurities of these ingredients as cosmetics, particularly percentage of actives in ingredients in fatty composition. And we wanted sensitization data on sodium lauroamphoacetate at max use concentration and I don't believe we've received that.

DR. ROSS: We didn't.

DR. COHEN: Yeah. So, again, just as a reminder of the 11 ingredients, disodium cocoamphodiacetate, disodium cocoamphodipropionate, sodium cocoamphoacetate, and sodium cocoamphopropionate have previously been reviewed as safe as used in a 1990 report which was rereviewed and reaffirmed in 2006. So, we needed feedback from the Read Across Group on this.

DR. ROSS: Yeah. So, I gave the last one so Susan, you want me to do this one or do you want to do this one?

DR. TILTON: We talked about some of the general read across concerns earlier already and with this group one of the primary concerns was doing read across for mixtures and the differences in composition across the different mixture groups. And then, also doing read across for certain sensitive endpoints. And in this case, that involved in some of the DART data that I'm sure we'll discuss.

DR. ROSS: There was a specific question on this betaine read across and there was a specific request that came in to reconsider that. I think that came from the consortium.

DR. TILTON: Specifically, for --

DR. ROSS: The betaine.

DR. TILTON: -- absorption.

DR. ROSS: Yeah. And so, the RAWG -- should we call it the RAWG or the Read Across Group? Anyway, the Read Across Group didn't support that so the betaine was not supported for read across. So basically, we hadn't changed our position on read across for two reasons. One being the mixtures that Susan pointed out and secondly the betaine was not supported. It's bitter ionic compound whereas the other ones, they're ionized also physiological ph. That's true, but only the betaines have a charged quaternary nitrogen in all PH values.

DR. COHEN: So, you couldn't take the betaine read across.

DR. ROSS: Correct.

DR. COHEN: Okay.

DR. ROSS: So that was that. You know, I think there are still concerns with the amphocarboxylates in general. The DART data and cardiac malformations. A new developmental toxicity study has been completed. We saw this document a few times, I believe, and the new DART data was always coming. Well, I think it's been completed now.

DR. COHEN: Didn't it say it was coming in September or October?

DR. ROSS: Yeah. And so, it'll be -- it's right now, I think, it's with Exponent, the consultants, and it'll be released to us in September/October as David comments. And I would just make the statement, which I do feel strongly about, you know, I wasn't strong on the yeast issues, but I do feel strongly about this one, that I think it's very unwise, in my opinion, to move ahead until we've seen that new DART data. So, I would support tabling this as well until December until we have a chance to look at that new DART data.

DR. COHEN: I had the same conclusion was to table until the December meeting because it said it would be available September/October which won't give us time.

DR. ROSS: Yeah. And I just think it would be very wise to do if we haven't seen that data.

MS. FIUME: Can I make a request? So, procedurally this is only a revised draft report and insufficient data announcement has never been issued yet. So, it is the Panel's prerogative to weigh on those data but also identify any other additional data needs to avoid that having to be the next step. And rather than table, if there are additional data needs, you can go out with an insufficient data announcement, then it would probably come back in December anyway and hopefully you would have those new data as well instead of having to wait and ask for additional data at that point if more is needed.

DR. COHEN: So, when -- I thought we had -- so, at June, we noted the following data are needed. I viewed that as an IDA. But maybe it wasn't an IDA.

MS. FIUME: Because it was tabled, there could be no true action. So, at times we'll know in the post/in the announcement as hey, industry, this hasn't been formally requested yet but this is what we're looking for. Just know that the Panel is also interested in this information.

DR. ROSS: Are you sure we can? Well, you know because you wrote it. But, I mean, did we not make that request?

MS. FIUME: It may have been asked for informally, but it hasn't been a formal --

DR. COHEN: So, it wasn't an IDA?

MS. FIUME: It wasn't an IDA. It was tabled which is why it came back as a revised draft report and not as a draft tentative report.

DR. COHEN: I think that makes a lot of sense. Otherwise, it's going to slow this process down a lot if we table to December, pick it up as a draft report -- well, it would be a draft --

MS. FIUME: Then it would be a revised draft report.

DR. COHEN: Revised draft report and it's going to take another year to get through.

DR. TILTON: So, this wouldn't be a tabling, this would be --

DR. COHEN: This would be an IDA.

DR. TILTON: -- an IDA and one of those requests would be for this data set that's coming forward.

DR. COHEN: So, let's line up our IDA then.

DR. ROSS: Yeah.

DR. BERGFELD: But you have a list already that you informally -- would you want to change that list? I mean --

DR. COHEN: I was just going to go through that with the group.

DR. ROSS: What's the PDF of that? I'm sorry, I'm just --

DR. COHEN: Well, it would be in the beginning.

DR. ROSS: Right in the beginning of the report, right.

DR. COHEN: Just look at the previous memo.

DR. ROSS: It should be there, right?

DR. COHEN: It's right on the first page. These memos are great.

DR. ROSS: Yeah, yeah. They're good. Yeah, yeah, yeah, yeah. I've got it. Got it, got it, got it. Yeah. Thanks. Yeah, there's the sensitization data on sodium lauroamphoacetate at max. We didn't get that. I would also like to see the, and we may not get this, but I'd like to see the ocular concentrations of use of the compounds that are used for that indication. We don't have concentrations of use in our use tables for those.

DR. COHEN: Okay. So, we still want dermal absorption data on what?

DR. BERGFELD: Sodium cocoamphopropionate.

DR. COHEN: We get to the table.

DR. ROSS: I think that's whether we're using read across to the betaine and --

DR. TILTON: Because we really don't have any data.

DR. ROSS: Yeah. So, I think you can just note that as dermal absorption data.

DR. COHEN: Say that again.

DR. ROSS: You could ask generically for dermal absorption data.

DR. COHEN: On the whole group?

DR. ROSS: Yeah. And then see what we get because I think it depends on the read across with -- if you're going to read across this point -- we're not.

DR. COHEN: So, none of these in this group are reading across to the others?

DR. ROSS: That's correct at this point.

DR. COHEN: That's pretty heavy.

DR. ROSS: Yeah. I think we have tox endpoints for most of the major compounds apart from DART. For most of the major compounds we have -- I think there's a way forward on many of these compounds that are used, at least the major ones -- and that, I think, we'd have to address when this comes up again. But I think all is not lost on this, I think there are potentially ways forward.

DR. COHEN: Okay. So dermal absorption data and we want DART.

DR. BERGFELD: Do you want the results of the DART? I mean, if they said they're doing it and it'll be ready, I mean, what --

DR. COHEN: This is for disodium cocoampho- --

DR. ROSS: Acetate, yeah.

DR. COHEN: -- -diacetate, right?

DR. TILTON: Diacetate, yes.

DR. ROSS: That's the compound where we had the cardiac malformation data. I think you could just leave it as is. DART data on disodium.

DR. COHEN: We'll keep that. We'll keep that. Further information regarding the composition and impurities of these ingredients.

DR. ROSS: Well, remember these things are listed as VC -- variable com- -- no, I've got that wrong. Anyway, their materials are listed at variable composition. I forget the actual definition. But that's what we were getting at with that comment. We wanted more definition around what's in them, but I think that we're going to get that because that's how they are. That's how they're made and that's how it's going to be. So, that was our request.

DR. COHEN: So, what's the disposition of the IDA for that?

DR. ROSS: I think we ask for it and if we can get it, that's great, because we need to know what's in there. I suspect we won't get it but that doesn't necessarily preclude a way forward. But it would be very good if we could point out what was actually in this study.

DR. COHEN: The sensitization at max use for sodium lauroamphoacetate.

DR. ROSS: I think that was 9.9 percent as I recall.

DR. COHEN: It was -- I thought it was 5.4 percent.

DR. ROSS: Ah, right. Max concentrations probably would be a safer way to go.

MS. FIUME: That's what we typically try to put into the post meeting announcement is just stating max concentration of use.

DR. COHEN: Yeah, max concentration.

MS. FIUME: Yeah.

DR. COHEN: There's a cocoamphoacetate at 20 percent in a rinse off product. The disodium lauroamphodiacetate has the highest concentration of use in a leave on product. So, I have one, two, three, four of the original plus ocular concentration of use in products used near the eye.

DR. ROSS: Yeah. That would be great, David, thank you.

DR. COHEN: Did I capture --

DR. ROSS: Yeah.

DR. COHEN: I like that idea of that we're not tabling it. This is just going to keep coming back around. So, this could come back anyway in December with that data anyway. That would be the course anyway and then we'd go to a draft tentative.

MS. FIUME: It would come in as a draft tentative report and go out as a tentative.

DR. COHEN: Yeah.

MS. FIUME: Yes.

DR. COHEN: Yeah.

DR. BERGFELD: What did you say about the eye? You wanted further documentation on this one, the concentrations in the eye? I note that there are some concentrations up to three percent.

DR. ROSS: Yeah, there are but there's --

DR. BERGFELD: That's up to 20 percent.

DR. ROSS: -- but in the eye a lot of them are not reported that are used around the eye.

MS. FIUME: Yeah, I believe it's those that -- the four that had been reviewed before have eye use, but no concentration given for them.

DR. ROSS: Yeah. So that was the only thing I needed, Wilma, just to --

DR. COHEN: Do we have a specific one for that, though? I'm trying to find it.

DR. ROSS: Well, there are -- I abbreviated these two numbers so -- in my report.

MS. FIUME: For those that are missing the concentration?

DR. ROSS: Yeah. For the eye area.

MS. FIUME: It's disodium cocoamphodiacetate, disodium cocoamphodipropionate, and sodium cocoamphoacetate. I have frequency of use for eye area products but not concentration. Did I miss any, Priya?

DR. ROSS: Which one --

DR. COHEN: Which PDF is that? Well, let me try to get to that PDF.

DR. ROSS: I have four compounds. Compounds one to four, but I'll have to get to my definitions.

DR. COHEN: Because you had a -- that chart is pretty useful.

DR. BERGFELD: So, if you had eye at 0.18 in one report and eye in another report of 1.3, are there other particular ingredients that's noted there is not reported would you not assume that they couldn't exceed what has been reported?

MS. FIUME: That is typically what happens, yeah.

DR. BERGFELD: So, the highest would be 1.3.

DR. COHEN: But if we can't read across does that still hold? That's a real bonified question. If you can't read across, does it matter that you've tagged a concentration of one, but you can't pull that data over to the other.

DR. BERGFELD: Well, that's a valid suggestion but that's all you have, so it probably shouldn't exceed that.

DR. COHEN: But how do we know that one's toxic at that concentration and not at the other if you're not reading across?

DR. ROSS: But you have, of the five most commonly used compounds there you've got three of them -- just provide notation here, one -- compounds one, three, and five we have in vitro ocular data at three percent. Compound five we have animals that meet compound one, we have humans at 1.2 percent and the maximum ocular concentration is 0.11 and 1.3 percent. It's already closed on one, three, five. So, three of the five compounds. So --

DR. COHEN: You're building, at least, a body of data to --

DR. ROSS: Yeah.

DR. COHEN: -- it's not a read across but it's culminating to safety.

DR. ROSS: So, it's like here we've got quite a few of these tox endpoints and many of them were frequently used compounds.

DR. COHEN: You still want the IDA?

DR. ROSS: Oh, yeah.

DR. COHEN: Okay.

MS. CHERIAN: So, for sensitization you want to just put sodium lauro?

DR. ROSS: Yeah.

DR. COHEN: For sodium lauroampho- --

MS. CHERIAN: Do you want specifically an HRIPT because we have LLNA data right now.

DR. COHEN: We have --

DR. BERGFELD: I don't think you ask specifically, you just ask for the sensitization data.

DR. COHEN: Can you just repeat what you just said?

MS. CHERIAN: If you wanted specifically an HRIPT because we have an LLNA and our maximum for leave on for that one I think is 1.1, but maximum for rinse off is 9.9.

DR. COHEN: Wait. I thought the maximum leave on for that was 5.4.

MS. CHERIAN: That's disodium lauroamphodiacetate.

DR. ROSS: It's 9.9.

MS. CHERIAN: For rinse off.

DR. COHEN: For rinse off.

MS. CHERIAN: The maximum leave on for all of these is 5.4 in disodium lauroamphodiacetate.

DR. COHEN: Disodium lauroamphodiacetate.

MS. CHERIAN: Mm-hmm.

DR. COHEN: So why is it? Let me just see something here. So why is our requested data different? You see in the memo? It's a sensitization data on sodium lauroamphoacetate at max use.

MS. CHERIAN: Well, we have data for disodium --

DR. ROSS: Isn't the max use 9.9? That's what I have in my notes. May be different.

DR. COHEN: Let me go back in my notes.

DR. ROSS: Let's go back to the table.

MS. FIUME: The highest leave on is 5.4. I think the 9.9 might be the rinse off.

DR. ROSS: Let's take a quick look, shall we?

MS. FIUME: Actually, I think -- I'm sorry -- the rinse off is 20 percent.

DR. COHEN: Yeah. I had it as 20 percent for cocoamphodiacetate. And the highest leave on was 5.4 percent for disodium lauroamphodiacetate. Is that wrong or is that old?

DR. ROSS: I just kept my dermal --

DR. COHEN: That's correct, what'd I just said? And our sensitization is way below that, right?

DR. ROSS: For sodium lauroampho, yeah.

DR. COHEN: Well, I'm looking at human.

DR. ROSS: For -- okay, so what I've got here, okay, for human with respect to the older data which I'm guessing this comes from previous reports, compound one which is the most common which is cocoamphodiacetate, for example, irritation in humans is okay to 25 percent and sensitization is okay at 35 percent.

DR. COHEN: But where are you?

DR. ROSS: This came from the old data.

DR. COHEN: I know, but what PDF are you in?

DR. ROSS: I don't have that in my notes.

DR. COHEN: I have human irritation, we have five percent for disodium cocoamphoacetate, right, for irritation in eight subjects.

DR. ROSS: Compare --

DR. COHEN: And then ten percent for sodium cocoamphoacetate.

DR. ROSS: Well, the old data I have summarized here.

DR. COHEN: I think these were a little irritated.

DR. BERGFELD: And they're detergents.

DR. COHEN: Yeah, they were moderate -- that's right, they're irritating. But for sensitization --

DR. BERGFELD: You have a guinea pig.

DR. COHEN: I see a guinea pig at --

DR. BERGFELD: You have irritations in humans.

DR. ROSS: You've got irritation/sensitization in humans.

DR. BERGFELD: Yeah.

DR. COHEN: Where's the sensitization? It's sodium lauroamphoacetate at 0.15. That's the only HRIPT I see.

DR. ROSS: Correct. Which is why we asked for that data. But the older data, Priya, tell me where that is on the PDF.

MS. CHERIAN: The summarized version is in italicized text.

DR. ROSS: Yeah. So that said -- at least I've got it in my notes and maybe I noted it incorrectly, but we were up at --

MS. FIUME: PDF Page 45.

DR. ROSS: Okay. Let's take a look because I've got it as high as 35 percent. PDF Page 45.

DR. COHEN: PDF 45.

DR. ROSS: Okay. And it should be italicized, correct?

MS. FIUME: HRIPTs are the second paragraph.

DR. COHEN: Ten percent. Is that not in the table?

MS. CHERIAN: No, because it's old data.

DR. ROSS: You don't put the older data in the table --

DR. TILTON: It's from when the first four were grouped so it doesn't include --

DR. COHEN: But we're not reading across, right? Again, what am I supposed to do with this if we're not reading across?

DR. ROSS: Well, you've got a list of --

DR. COHEN: Just reminded me, do we have this report in there?

MS. CHERIAN: (Inaudible).

DR. ROSS: I didn't have --

MS. FIUME: (Inaudible) sodium cocoamphodiacetate. That HRIPT; the last sentence.

DR. COHEN: Give me that again.

MS. FIUME: The last sentence with the italicized text with the HRIPTs it says in addition the sensitization was observed in an HRIPT using disodium cocoamphodiacetate, 32 percent solids, under semi occlusive conditions. However, some irritation was noted under occlusive conditions.

DR. COHEN: That's good.

DR. ROSS: The maximum use, I believe, is 20 percent. So --

DR. COHEN: So, that's the disodium cocoamphodiacetate and we asked for sodium lauroamphoacetate, right?

MS. FIUME: Yeah.

DR. ROSS: Yeah.

MS. FIUME: Yeah. So --

DR. COHEN: And there's a report of disodium lauroamphodiacetate allergy in the literature at one and two percent patch testing.

DR. ROSS: So, you definitely need that.

DR. COHEN: I'd like to have it.

DR. ROSS: I think -- it looks to me --

DR. COHEN: Let me see if I can find it again.

MS. CHERIAN: If you look on 26.

DR. ROSS: So, the cocoamphodiacitates, I have the maximum use at 20 percent. Irritation was okay from the older data at 25 percent. Sensitization was okay at 32 percent. So that one I thought was okay.

DR. COHEN: So, are we continuing the IDA with what we had?

DR. ROSS: I think so and then we work through these issues of what we need with respect to when it comes in. If we assume no read across, I mean, I think you can clear, at least by my notes, disodium cocoamphodiacetate on the dermal and sodium cocoamphoacetate on the dermal based on all the data we have and the concentrations that are used. We still have data gaps with some of the other compounds including the sodium lauroamphoacetate which you are asking for specifically in the IDA.

DR. COHEN: Okay. Hold on a second. So, were you clearing the original four that were cleared?

DR. ROSS: What were the original four that were cleared?

DR. COHEN: Disodium cocoamphoacetate, disodium cocoamphodipropionate, sodium cocoamphoacetate, and sodium cocoamphopropionate.

DR. ROSS: Clearing in what respect? Just on the ocular end?

DR. COHEN: No, just for everything.

DR. ROSS: No, I wasn't clearing anything.

DR. COHEN: Okay.

MS. CHERIAN: That was in there.

DR. COHEN: That was in there.

MS. CHERIAN: It's 38.

DR. COHEN: It's number 38. Okay.

MS. FIUME: So, I can prepare you for Don tomorrow?

DR. COHEN: What's that again.

MS. FIUME: I said I can prepare you for Don tomorrow. It's PDF Page 65. So those --

DR. COHEN: PDF 65.

MS. FIUME: Right, because you're asking for sodium lauroamphoacetate. So those sensitization studies are not sufficient.

DR. COHEN: Hold on. Let me clear this because I'm not getting the page numbers. Okay. Here?

MS. FIUME: Yes.

DR. COHEN: Sodium lauroamphoacetate is at 0.15 percent for humans as opposed to 5.4 percent. So, and then let me look at the others. Are you going to --

MS. FIUME: There's -- the animal studies in there.

DR. COHEN: Yeah, I know he's going to -- I know that -- I know it --

MS. FIUME: As I said, I'm preparing you for tomorrow.

DR. COHEN: Positive reactions were observed in 5 in 20 test animals during challenge. Positive.

MS. FIUME: But the study was deemed unsensitive and I don't remember why. The substance was classified to be non-sensitive

DR. ROSS: Non-sensitizing, yeah. But 5 of 20 test animals.

MS. FIUME: I know. Yeah. I read the last part first.

DR. ROSS: But the induction was only done with half percent, and the challenge was 20 percent.

DR. COHEN: Right. Yeah. It's, yeah. So, we can have that discussion tomorrow. It's definitely coming. I saw the launch before it happened, but we'll see.

DR. ROSS: So, the IDA basically stands.

DR. COHEN: Yeah.

DR. ROSS: Okay.

MS. CHERIAN: But would you like the addition of the disodium lauroamphodiacetate at 5.4 percent for sensitization because of that liquid hand soap study?

DR. COHEN: So, the liquid soap study is disodium lauroamphodiacetate.

MS. CHERIAN: Mm-hmm.

DR. COHEN: What's its max use?

MS. CHERIAN: 5.4.

DR. COHEN: That was 5.4?

DR. ROSS: I thought it was 9.9.

MS. CHERIAN: Oh, 5.4 for disodium lauroamphodiacetate for leave on.

MS. FIUME: Rinse off because that's not typically used at max concentration in HRIPTs.

DR. COHEN: So, what's the sodium -- what's the max use of sodium lauroamphoacetate?

MS. FIUME: It's usually the leave ons has been what the Panel has typically done.

DR. COHEN: Okay.

MS. CHERIAN: I think 1.1 in leave on and 9.9 in rinse off.

DR. COHEN: This one's 9.9 --

MS. CHERIAN: Rinse off.

DR. COHEN: Rinse off -- and what?

MS. CHERIAN: 1.1 from what I remember, I think. Yes, 1.1.

DR. COHEN: Leave on. And then we're amending the IDA for disodium, right?

MS. CHERIAN: You can still ask for sodium lauroamphoacetate too.

DR. COHEN: Yeah. We still will.

MS. CHERIAN: Okay. But I think you want sodium lauroamphodiacetate at max use of 5.4.

MS. FIUME: 5.4 is the disodium lauroamphodiacetate. It's a leave on hair product.

DR. ROSS: Oh, okay.

DR. COHEN: Acetate at 5.4 percent.

MS. FIUME: Mm-hmm.

DR. COHEN: Yep, okay. Good. That extra discussion helped. Any other further comments on the amphocarboxylates?

DR. BERGFELD: I'm sorry, I'm going to just ask you to summarize what you're going to say.

DR. COHEN: No, that's perfectly fine. So, we're going to come out with an IDA for dermal absorption data on the whole group. DART on disodium cocoamphodiacetate. Further information on composition and impurities of these ingredients in cosmetics. Sensitization data on sodium lauroamphoacetate at max use, which is 9.9 in rinse off, 1.1 in leave on. Sensitization data on disodium laurodiacetate up to 5.4 percent. Ocular concentrations of use of products used near the eye that don't have them listed now.

DR. BERGFELD: So, you're actually on the sensitization on sodium lauro, going to give a concentration of 5.4 or a max --

DR. COHEN: No. I'm just going to say max use.

DR. BERGFELD: Okay.

DR. COHEN: That was just for our -- because we might have a discussion tomorrow and the need for the concentrations at hand may be necessary. Okay. Let me just check that one off. I don't know if we're a third of the way through.

DR. ROSS: Downhill from here.

DR. COHEN: I'd like to think so.

Full Panel – June 4, 2023

DR. COHEN: This is a Revised Draft Report on the safety assessment of Fatty Amphocarboxylates. This report was reviewed at the June 2023 meeting at which time the Panel tabled the review due to receipt of data received in Wave 2. These data include information regarding various fatty acid chain mixtures that comprised ingredients reviewed in this report and REACH dossiers for some of the substances.

The read-across coterie members on this team expressed apprehension regarding some of the following. The apprehension on the read-across was problems reading across for mixtures, reading across for certain endpoints like DART which they found concerning, and read-across for the betaines which was not supported.

So our motion, given these read-across headwinds, is an Insufficient Data Announcement with the following needs: dermal absorption data for the whole group, DART data on Disodium Cocoamphodiacetate which we understand is due to be completed in September-October, further information regarding the composition and impurities of these ingredients in cosmetics particularly percentage of actives in ingredients and fatty acid compositions, sensitization data on Sodium Lauroamphoacetate at max use and Disodium Lauroamphoacetate which is the highest concentration of use reported in leave-on products, and ocular concentration of use in products used around the eye. That's my motion. I'm sure there will be some discussion.

DR. BELSITO: Well, you had a lot more insufficiencies than we did, number one. Number two, I think, again, the read-across needs to go to the Read-Across Working Group. Concerning the betaine, I think it's important that read-across is endpoints specific and they were looking at that just for absorption, and not for other endpoints. And that the use of the betaine for the absorption was approved by ECHA, so there are other authorities who have accepted that as a read-across for absorption.

I'm not sure that we need sensitization data. We have data in the report I think that clears that. It can be irritating, and of course that would end up in our conclusion. If we found these safe as used they'd be formulated to be nonirritating. You said you want absorption on all of them?

DR. COHEN: I don't think we have absorption on any of them.

DR. BELSITO: But, you're asking for absorption on each and every one in the group?

DR. COHEN: Well, so, Don, if there's no read-across on these --

DR. BELSITO: But we don't know that yet.

DR. COHEN: I was under the impression that we couldn't do much read-across.

DR. RETTIE: For the betaines initial meeting of the working group, we're really not in favor of that at all for the betaines for arguments related to differing ionization across the pH range. Which is not an issue for the betaines, but they do vary for the other compounds. So we need to go back and take a closer look at that.

I had a comment about read-across as it relates to mixtures. In the working group we had a strong feeling that that was a complication. And I still think for two mixtures it's a complication that we have to acknowledge exists. But for this particular group of compounds that we're looking at here, just over the last day I've seen my attention has been drawn to citations that abrogate a lot of my concerns about heterogeneity. My concerns about heterogeneity were at the level of monoacetates and diacetates being in the same preparation.

It would appear that there is another view on this, that in fact the compounds at the level of monoacetates, diacetates, monopropionates, dipropionates, is pretty pure. The confusion as I had in my head seems to exist at the level of a wrong hypothesis being proposed for how these things were synthesized.

Now, in the exponent report there's a reference to a foreign book chapter, which my team have now to take a look at in detail. And that really lays out another view of those impurities, vis-à-vis, no impurities at the level of the monoacetate versus diacetate, etcetera.

I still think we have some level of heterogeneity, of course, the level of the different e-cell site chains that comes from the oils that are being use. But that's just inherent in there, and this group has seen that in the alcohol betaines and probably other reports in the past. And given that by far the major constituent there is the C12, we know a quite a bit about it. And so a lot of these impurities concerns that I was raising yesterday have fallen away for me. And I think we're dealing with a more homogenous group than I originally thought.

DR. ROSS: If I can just make a comment that we haven't seen that paper or papers you're referring to, Allan.

DR. RETTIE: I emailed it to you at 12:02 last night.

DR. ROSS: Oh, I stand corrected. But, I think the RAW Group needs to consider that again. I think it wasn't just you that was "confused" on the composition and impurities of these things. I think that was a joint RAWG decision. And it appeared to us these were variable composition biomaterials that basically have -- and the components of these mixtures had very different physical properties. So you're looking at solubility and LogPs. It's an order of magnitude different. And so a lot of the conclusion was predicated on that analysis. Now, if that's different, then I think the RAW Group needs to look at that again.

DR. RETTIE: Absolutely. I feel it's different, and you'll be able to assess that with this foreign document that you now have.

DR. ROSS: I look forward to reading it on the plane at 12:02 -- no, okay.

DR. BELSITO: Don, on PDF 65, in animal sensitization, there seems in the results to be signals there. And, there's a case report on contact sensitization to Disodium Lauroamphoacetate where they patch tested it at one and two percent it was positive. So I think this early in the game with the animal, right, you see in Table 10?

DR. BELSITO: Yes.

DR. COHEN: So, I thought having some more sensitization, whether that be animal in silco, or HRIPT, getting this dossier a little bit more beefed up in sensitization would be helpful.

DR. BELSITO: Well, we have to be careful. I mean, we can't ask for new animal data, right.

DR. COHEN: No, no, they just may be out there, right, and we don't need to ask for new animal data.

DR. BELSITO: I mean, we think it's insufficient based upon definitely the genotox. Curt looked at the exponent report and it actually were two of three studies showing some cardiac abnormalities. So we look forward to the report that's promised. So we have no problem going out with insufficiencies. If you want to add your insufficiencies, we've done this before. We can eliminate them when we look at them later on, so I'm fine.

DR. COHEN: Did you want to add your geno? I don't know if I'm -- I mentioned DART.

DR. BELSITO: I think you mentioned the study that has been promised on the DART endpoints, but if not, yeah, I think that's the biggest data point that we need.

DR. COHEN: It's in there.

DR. ROSS: There is another paper as Don points out. There are at least two or three of those studies. I think I pointed this out last time that that should be added to our Discussion. I think that reference was Greens, et al 2022, with the cardiac malformations and the DART data.

DR. COHEN: Okay.

DR. BERGFELD: So we have a motion and a second that we're going out for an IDA. Do we have a list of things that are needed, David?

DR. COHEN: Yeah.

DR. BERGFELD: Great discussion. I call the question, all those in favor of this conclusion? Thank you, very much. And, Paul, I'm assuming you agree?

DR. SNYDER: I concur.

DR. BERGFELD: Okay, thank you. Okay, moving on to Inositol, Dr. Belsito.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: August 5, 2024

SUBJECT: Additional Information from the REACH Amphoacetates Consortium on the Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics

Thank you very much for the opportunity to provide additional information to address the requested data.

Skin Sensitization

Please find enclosed the prediction reports of the OECD QSAR Toolbox Skin Sensitisation Automated Workflow for Defined Approaches on Skin Sensitisation (SS AW for DASS). This prediction tool has been reviewed and assessed by an OECD Expert Group for the use in a Defined Approach to contribute to the prediction of skin sensitisation potential of a chemical substance (OECD Series on Testing & Assessment No. 336). Based on the DASS Reference Dataset, the method was assigned a sensitivity of 94 % as compared to LLNA test results, and 92 % as compared with a human dataset. The specificity of the prediction is 73 % and 56 %, respectively. The method has been implemented in OECD Guideline 497 (Defined Approaches for Skin Sensitisation) accordingly. Predictions were conducted with the four constituents stated in Figure 2 of the submitted Read-Across Justification Document for Amphoacetates.

All predictions were negative and within the applicability domain. Based on the reported performance metrics (see above), the predictions can be considered highly reliable and sensitive.

Attachments:
C12 Diacetate 1 Prediction Report
C12 Diacetate 2 Prediction Report
C12 Monoacetate 1 Prediction Report
C12 Monoacetate 2 Prediction Report

Developmental and Reproductive Toxicity

As mentioned earlier, a prenatal developmental toxicity study (OECD TG 414) in rabbits and an Extended One-Generation Reproduction Toxicity Study (OECD TG 443) were contracted for Amphoacetates C8-C18 (Diacetate form) to address Standard Information Requirements under REACH. We expect all study reports to be finalised by end of April 2025 and would be ready to provide you with robust study summaries by that date; several months before they are made publicly available on ECHA website.

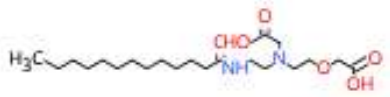
Meanwhile, we would like to point you towards studies that seem to be missing from the section "Developmental and Reproductive Toxicity Studies" and table 10 of the updated draft CIR:
As with Disodium Cocoamphodiacetate (Amphoacetates C8-C18, diacetate form) and Sodium Lauroamphoacetate (Amphoacetates C12, monoacetate form), a prenatal developmental toxicity study (OECD TG 414) (including extended dose range finder) was conducted with Amphoacetates C12-C14 (Diacetate form, EC No. 938-645-3). This information was shared earlier, but we acknowledge that due to the overwhelming amount of information shared last time, these studies might be missed. We kindly refer to the REACH dossier of this substance. In the same dossier, you will also find a sub-chronic oral toxicity study (OECD TG 408) in Wistar rats with this substance.

Overall, we believe that we can fill substantial data gaps for DART by the end of April next year. We would therefore propose to the Expert Panel to consider tabling the finalisation of the CIR until their meeting in June 2025, so that the assessment of this additional information can be included in the report.

Read-across prediction report

Toolbox version: 4.6
Date: 5 Aug 2024
Author(s):
Contact details:

Target information

Structural information	Numerical identifiers	Chemical names
SMILES: CCCCCCCCCCCCC(=O)NCCN(CCOCC(O)=O)CC(O)=O Structure 	CAS#: No CAS number Other: N/A	

Prediction summary

Predicted endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Predicted value: Negative [Skin sensitisation II (ECETOC)]

Data gap filling method: Read-across analysis, Automated workflow for EC3 from LLNA or Skin sensitization from GPMT assays for defined approaches (SS AW for DASS)

Applicability domain: In domain

Summary: *manually editable field*
Diacetate Form 1 (C12-Amphoacetates) was predicted to be non-sensitising based on read-across.
The prediction is in-domain.

Detailed information on analogues and data used for data gap filling is included in the attached Data matrix.

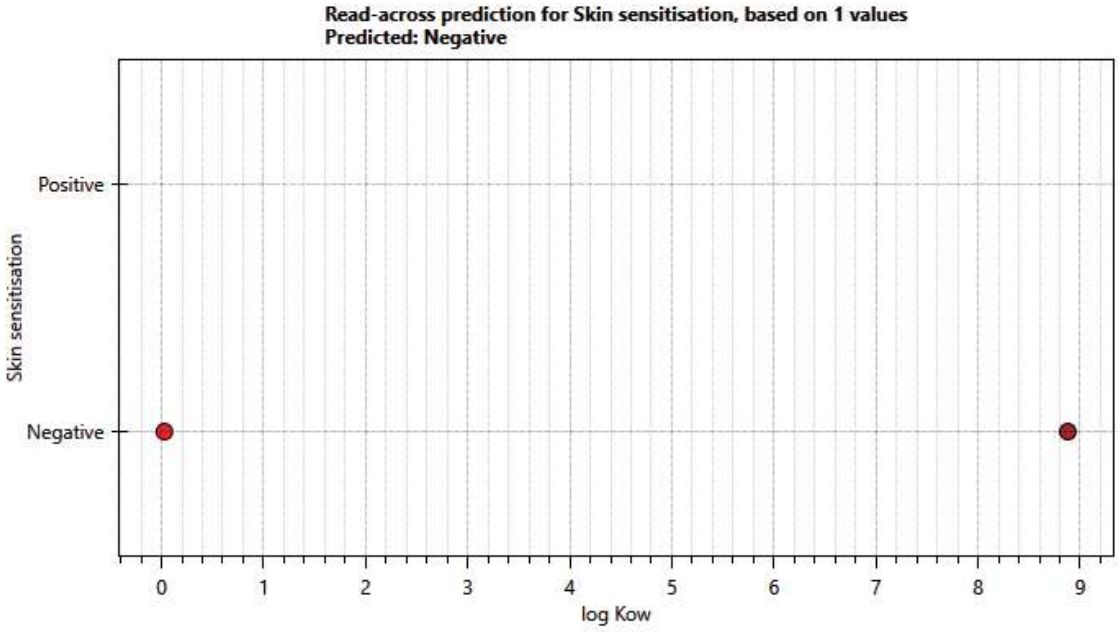
Prediction details

Predicted value: Negative [Skin sensitisation II (ECETOC)]

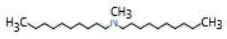
Applicability domain: In domain (DASS Overall domain: Negative-read-across)

Predicted endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Prediction plot:



Values used for the prediction:

Structure	Experimental values used for the prediction (Maximal)	log Kow
CAS: 7396-58-9 SMILES: CCCCCCCCCCN(C)CCCCCCCCCC Name: N-Methyldidecylamine 	Negative	8,88

Calculation approach: takes the highest mode value from the 1 nearest neighbours

Active descriptor: log Kow (calculated)

Data usage: Maximal value*

*When multiple values are available for the same chemical, their maximal value is taken in prediction calculations

Prediction protocol
(Inclusion criteria)

Input: SMILES: CCCCCCCCCCCCC(=O)NCCN(CCOCC(O)=O)CC(O)=O

Database(s) used:

- REACH Skin sensitisation database (normalised)
- Skin Sensitization

Selected endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Categorisation:

Primary categorisation

Profiler: US-EPA New Chemical Categories (not strict)
Target: Aliphatic Amines
Selection: Aliphatic Amines
Category: 206 chemicals with 259 experimental data

Sub-categorization steps

- Step 1: Data usage options are changed to: Maximal

Sub-category: 171 chemicals with 234 experimental data

- Step 2:

Profiler: Substance type
Target: Discrete chemical; Mono constituent (predefined); Organic
Selection: Substances different from target are removed
Sub-category: 148 chemicals with 208 experimental data

- Step 3:

Profiler: Protein binding alerts for skin sensitization by OASIS
Target: No alert found
Selection: Substances different from target are removed
Sub-category: 136 chemicals with 195 experimental data

- Step 4:

Profiler: Protein binding alerts for skin sensitization by OASIS combined with Autoxidation simulator
Target and metabolites: No alert found
Selection: Substances different from target are removed
Sub-category: 124 chemicals with 182 experimental data

- Step 5:

Profiler: Protein binding alerts for skin sensitization by OASIS combined with Skin metabolism simulator
Target and metabolites: No alert found
Selection: Substances different from target are removed
Sub-category: 47 chemicals with 61 experimental data

- Step 6:
Profiler: Protein binding potency GSH
Target: Not possible to classify according to these rules (GSH)
Selection: Substances different from target are removed
Sub-category: 44 chemicals with 58 experimental data

- Step 7:
Profiler: Organic functional groups, Norbert Haider (checkmol)
Target: Amine; Carboxylic acid; Carboxylic acid amide; Carboxylic acid derivative; Carboxylic acid sec. amide; Dialkylether; Ether; Tertiary aliphatic amine; Tertiary amine
Selection: Substances different from target are removed
Sub-category: 5 chemicals with 5 experimental data

- Step 8:
Profiler: Structure similarity
Target: [90%,100%]
Selection: Substances different from target are removed except [50%,60%)
Sub-category: 2 chemicals with 1 experimental data

Data gap filling:
Calculation approach: takes the highest mode value from the 1 nearest neighbours, Active descriptor: log Kow (calculated), Data usage: Maximal value

References and explanations

Database information:

- REACH Skin sensitisation database (normalised)

Profilers information:

- Protein binding potency GSH
- Protein binding alerts for skin sensitization by OASIS
- Keratinocyte gene expression
- Substance type
- US-EPA New Chemical Categories

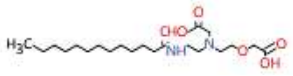
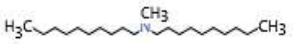
Profilers result information:

- Discrete chemical (Substance type)
- Organic (Substance type)
- Mono constituent (predefined) (Substance type)
- Aliphatic Amines (US-EPA New Chemical Categories)

Appendix: Specific report explanations

Specific information regarding the prediction

Table with profiling results for "Organic functional groups"

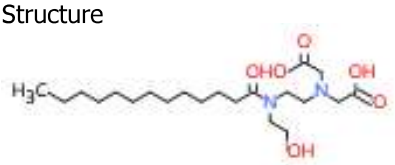
CAS	Structure	Results
1 CAS# No CAS number		Amine, tertiary Ether moiety Carboxylic acid Organic amide and thioamide Aliphatic amine, tertiary
2 CAS# 7396-58-9		Amine, tertiary Aliphatic amine, tertiary

Structural functionalities, different from the target are colored in red.

Read-across prediction report

Toolbox version: 4.6
Date: 5 Aug 2024
Author(s):
Contact details:

Target information

Structural information	Numerical identifiers	Chemical names
SMILES: CCCCCCCCCCCCC(=O)N(CCO)CCN(CC(O)=O)CC(O)=O Structure 	CAS#: No CAS number Other: N/A	

Prediction summary

Predicted endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Predicted value: Negative [Skin sensitisation II (ECETOC)]

Data gap filling method: Read-across analysis, Automated workflow for EC3 from LLNA or Skin sensitization from GPMT assays for defined approaches (SS AW for DASS)

Applicability domain: In domain

Summary: *manually editable field*
Diacetate Form 2 (C12-Amphoacetates) was predicted to be non-sensitising based on read-across.
The prediction is in-domain.

Detailed information on analogues and data used for data gap filling is included in the attached Data matrix.

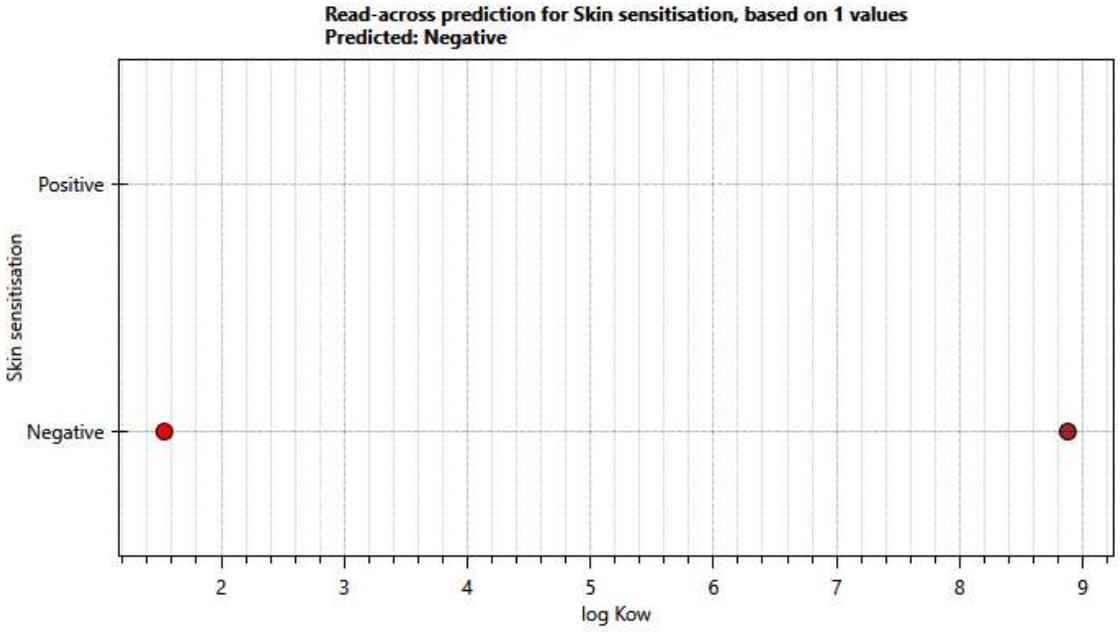
Prediction details

Predicted value: Negative [Skin sensitisation II (ECETOC)]

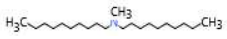
Applicability domain: In domain (DASS Overall domain: Negative-read-across)

Predicted endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Prediction plot:



Values used for the prediction:

Structure	Experimental values used for the prediction (Maximal)	log Kow
CAS: 7396-58-9 SMILES: CCCCCCCCCCN(C)CCCCCCCCCC Name: N-Methyldidecylamine 	Negative	8,88

Calculation approach: takes the highest mode value from the 1 nearest neighbours

Active descriptor: log Kow (calculated)

Data usage: Maximal value*

*When multiple values are available for the same chemical, their maximal value is taken in prediction calculations

Prediction protocol
(Inclusion criteria)

Input: SMILES: CCCCCCCCCCCCC(=O)N(CCO)CCN(CC(O)=O)CC(O)=O

Database(s) used:
- REACH Skin sensitisation database (normalised)
- Skin Sensitization

Selected endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Categorisation:

Primary categorisation

Profiler: US-EPA New Chemical Categories (not strict)
Target: Aliphatic Amines
Selection: Aliphatic Amines
Category: 206 chemicals with 259 experimental data

Sub-categorization steps

- Step 1: Data usage options are changed to: Maximal

Sub-category: 171 chemicals with 234 experimental data

- Step 2:

Profiler: Substance type
Target: Discrete chemical; Mono constituent (predefined); Organic
Selection: Substances different from target are removed
Sub-category: 148 chemicals with 208 experimental data

- Step 3:

Profiler: Protein binding alerts for skin sensitization by OASIS
Target: No alert found
Selection: Substances different from target are removed
Sub-category: 136 chemicals with 195 experimental data

- Step 4:

Profiler: Protein binding alerts for skin sensitization by OASIS combined with Autoxidation simulator
Target and metabolites: No alert found
Selection: Substances different from target are removed
Sub-category: 124 chemicals with 182 experimental data

- Step 5:

Profiler: Protein binding alerts for skin sensitization by OASIS combined with Skin metabolism simulator
Target and metabolites: No alert found
Selection: Substances different from target are removed
Sub-category: 47 chemicals with 61 experimental data

- Step 6:
Profiler: Protein binding potency GSH
Target: Not possible to classify according to these rules (GSH)
Selection: Substances different from target are removed
Sub-category: 44 chemicals with 58 experimental data

- Step 7:
Profiler: Organic functional groups, Norbert Haider (checkmol)
Target: Alcohol; Amine; Carboxylic acid; Carboxylic acid amide; Carboxylic acid derivative; Carboxylic acid tert. amide; Hydroxy compound; Primary alcohol; Tertiary aliphatic amine; Tertiary amine
Selection: Substances different from target are removed
Sub-category: 9 chemicals with 16 experimental data

- Step 8:
Profiler: Structure similarity
Target: [90%,100%]
Selection: Substances different from target are removed except [50%,60%)
Sub-category: 2 chemicals with 1 experimental data

Data gap filling:
Calculation approach: takes the highest mode value from the 1 nearest neighbours, Active descriptor: log Kow (calculated), Data usage: Maximal value

References and explanations

Database information:

- REACH Skin sensitisation database (normalised)

Profilers information:

- Protein binding potency GSH
- Protein binding alerts for skin sensitization by OASIS
- Keratinocyte gene expression
- Substance type
- US-EPA New Chemical Categories

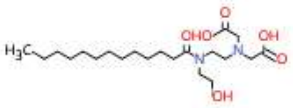
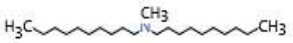
Profilers result information:

- Discrete chemical (Substance type)
- Organic (Substance type)
- Mono constituent (predefined) (Substance type)
- Aliphatic Amines (US-EPA New Chemical Categories)

Appendix: Specific report explanations

Specific information regarding the prediction

Table with profiling results for "Organic functional groups"

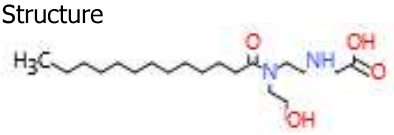
CAS	Structure	Results
1 CAS# No CAS number		Alcohol Amine, tertiary Carboxylic acid Organic amide and thioamide Aliphatic amine, tertiary
2 CAS# 7396-58-9		Amine, tertiary Aliphatic amine, tertiary

Structural functionalities, different from the target are colored in red.

Read-across prediction report

Toolbox version: 4.6
Date: 5 Aug 2024
Author(s):
Contact details:

Target information

Structural information	Numerical identifiers	Chemical names
SMILES: CCCCCCCCCCCCC(=O)N(CCO)CCNCC(O)=O Structure 	CAS#: No CAS number Other: N/A	

Prediction summary

Predicted endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Predicted value: Negative [Skin sensitisation II (ECETOC)]

Data gap filling method: Read-across analysis, Automated workflow for EC3 from LLNA or Skin sensitization from GPMT assays for defined approaches (SS AW for DASS)

Applicability domain: In domain

Summary: *manually editable field*
Monoacetate Form 1 (C12-Amphoacetates) was predicted to be non-sensitising based on read-across.
The prediction is in-domain.

Detailed information on analogues and data used for data gap filling is included in the attached Data matrix.

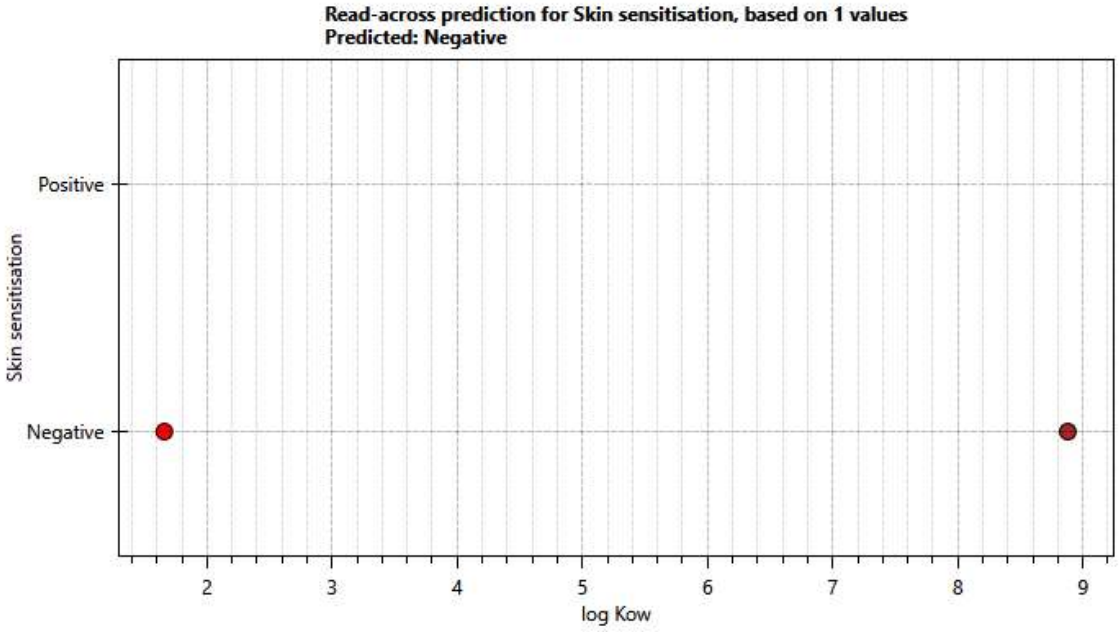
Prediction details

Predicted value: Negative [Skin sensitisation II (ECETOC)]

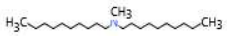
Applicability domain: In domain (DASS Overall domain: Negative-read-across)

Predicted endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Prediction plot:



Values used for the prediction:

Structure	Experimental values used for the prediction (Maximal)	log Kow
CAS: 7396-58-9 SMILES: CCCCCCCCCCN(C)CCCCCCCCCC Name: N-Methyldidecylamine 	Negative	8,88

Calculation approach: takes the highest mode value from the 1 nearest neighbours

Active descriptor: log Kow (calculated)

Data usage: Maximal value*

*When multiple values are available for the same chemical, their maximal value is taken in prediction calculations

Prediction protocol
(Inclusion criteria)

Input: SMILES: CCCCCCCCCCCCC(=O)N(CCO)CCNCC(O)=O

Database(s) used:
- REACH Skin sensitisation database (normalised)
- Skin Sensitization

Selected endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Categorisation:

Primary categorisation

Profiler: US-EPA New Chemical Categories (not strict)
Target: Aliphatic Amines
Selection: Aliphatic Amines
Category: 206 chemicals with 259 experimental data

Sub-categorization steps

- Step 1: Data usage options are changed to: Maximal

Sub-category: 171 chemicals with 234 experimental data

- Step 2:

Profiler: Substance type
Target: Discrete chemical; Mono constituent (predefined); Organic
Selection: Substances different from target are removed
Sub-category: 148 chemicals with 208 experimental data

- Step 3:

Profiler: Protein binding alerts for skin sensitization by OASIS
Target: No alert found
Selection: Substances different from target are removed
Sub-category: 136 chemicals with 195 experimental data

- Step 4:

Profiler: Protein binding alerts for skin sensitization by OASIS combined with Autoxidation simulator
Target and metabolites: No alert found
Selection: Substances different from target are removed
Sub-category: 124 chemicals with 182 experimental data

- Step 5:

Profiler: Protein binding alerts for skin sensitization by OASIS combined with Skin metabolism simulator
Target and metabolites: No alert found
Selection: Substances different from target are removed
Sub-category: 47 chemicals with 61 experimental data

- Step 6:
Profiler: Protein binding potency GSH
Target: Not possible to classify according to these rules (GSH)
Selection: Substances different from target are removed
Sub-category: 44 chemicals with 58 experimental data

- Step 7:
Profiler: Organic functional groups (US EPA)
Target: Acid, aliphatic attach [-COOH]; Alcohol, olefinic attach [-OH]; Aliphatic Carbon [-CH2-]; Aliphatic Carbon [-CH3]; Aliphatic Carbon [CH]; Amide, aliphatic attach [-C(=O)N]; Amino-carbonyl compound [NCC(=O)-C]; Amino, aliphatic attach [-N<]; Amino, aliphatic attach [-NH-]; Carbonyl, aliphatic attach [-C(=O)-]; Hydroxy, aliphatic attach [-OH]; Miscellaneous sulfide (=S) or oxide (=O); Olefinic carbon [=CH- or =C<]
Selection: Substances different from target are removed
Sub-category: 8 chemicals with 14 experimental data

- Step 8:
Profiler: Structure similarity
Target: [90%,100%]
Selection: Substances different from target are removed except [50%,60%)
Sub-category: 2 chemicals with 1 experimental data

Data gap filling:
Calculation approach: takes the highest mode value from the 1 nearest neighbours, Active descriptor: log Kow (calculated), Data usage: Maximal value

References and explanations

Database information:

- REACH Skin sensitisation database (normalised)

Profilers information:

- Protein binding potency GSH
- Protein binding alerts for skin sensitization by OASIS
- Keratinocyte gene expression
- Substance type
- US-EPA New Chemical Categories

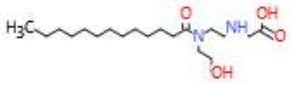
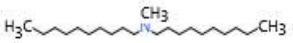
Profilers result information:

- Discrete chemical (Substance type)
- Organic (Substance type)
- Mono constituent (predefined) (Substance type)
- Aliphatic Amines (US-EPA New Chemical Categories)

Appendix: Specific report explanations

Specific information regarding the prediction

Table with profiling results for "Organic functional groups"

CAS	Structure	Results
1 CAS# No CAS number		Alcohol Amine, secondary Carboxylic acid Organic amide and thioamide Aliphatic amine, secondary
2 CAS# 7396-58-9		Amine, tertiary Aliphatic amine, tertiary

Structural functionalities, different from the target are colored in red.

Read-across prediction report

Toolbox version: 4.6
Date: 5 Aug 2024
Author(s):
Contact details:

Target information

Structural information	Numerical identifiers	Chemical names
SMILES: CCCCCCCCCCCCC(=O)NCCN(CCO)CC(O)=O Structure 	CAS#: No CAS number Other: N/A	

Prediction summary

Predicted endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Predicted value: Negative [Skin sensitisation II (ECETOC)]

Data gap filling method: Read-across analysis, Automated workflow for EC3 from LLNA or Skin sensitization from GPMT assays for defined approaches (SS AW for DASS)

Applicability domain: In domain

Summary: *manually editable field*
Monoacetate Form 2 (C12-Amphoacetates) was predicted to be non-sensitising based on read-across.
The prediction is in-domain.

Detailed information on analogues and data used for data gap filling is included in the attached Data matrix.

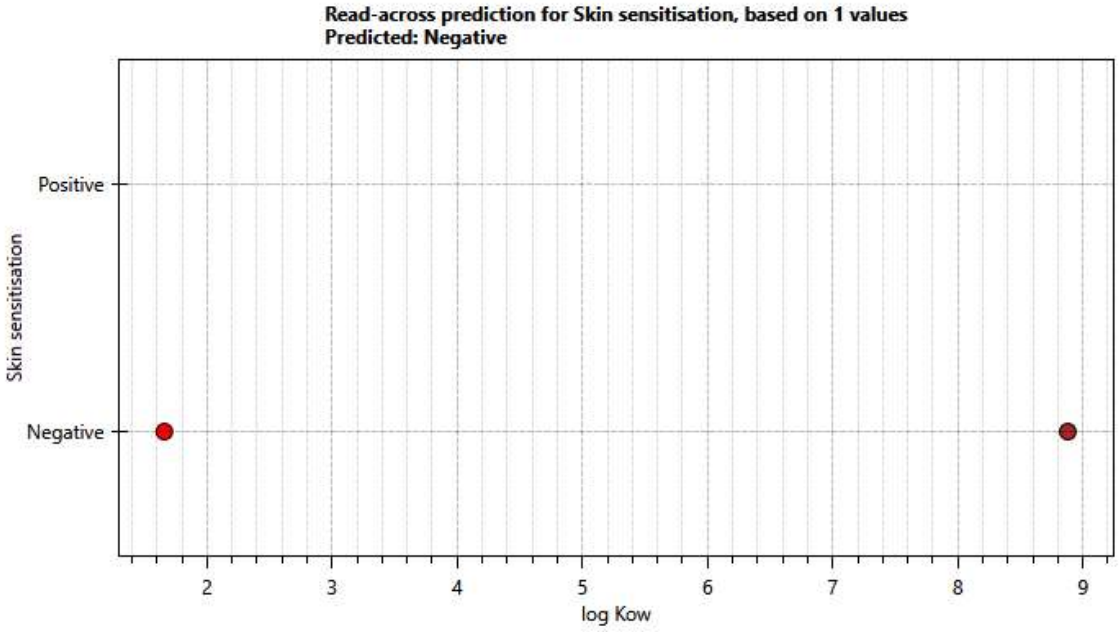
Prediction details

Predicted value: Negative [Skin sensitisation II (ECETOC)]

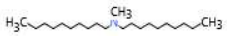
Applicability domain: In domain (DASS Overall domain: Negative-read-across)

Predicted endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Prediction plot:



Values used for the prediction:

Structure	Experimental values used for the prediction (Maximal)	log Kow
CAS: 7396-58-9 SMILES: CCCCCCCCCCN(C)CCCCCCCCCC Name: N-Methyldidecylamine 	Negative	8,88

Calculation approach: takes the highest mode value from the 1 nearest neighbours

Active descriptor: log Kow (calculated)

Data usage: Maximal value*

*When multiple values are available for the same chemical, their maximal value is taken in prediction calculations

Prediction protocol
(Inclusion criteria)

Input: SMILES: CCCCCCCCCCCCC(=O)NCCN(CCO)CC(O)=O

Database(s) used:
- REACH Skin sensitisation database (normalised)
- Skin Sensitization

Selected endpoint: Human Health Hazards -> Sensitisation -> Skin -> in Vivo -> GPMT -> Skin sensitisation

Categorisation:

Primary categorisation

Profiler: US-EPA New Chemical Categories (not strict)
Target: Aliphatic Amines
Selection: Aliphatic Amines
Category: 206 chemicals with 259 experimental data

Sub-categorization steps

- Step 1: Data usage options are changed to: Maximal

Sub-category: 171 chemicals with 234 experimental data

- Step 2:

Profiler: Substance type
Target: Discrete chemical; Mono constituent (predefined); Organic
Selection: Substances different from target are removed
Sub-category: 148 chemicals with 208 experimental data

- Step 3:

Profiler: Protein binding alerts for skin sensitization by OASIS
Target: No alert found
Selection: Substances different from target are removed
Sub-category: 136 chemicals with 195 experimental data

- Step 4:

Profiler: Protein binding alerts for skin sensitization by OASIS combined with Autoxidation simulator
Target and metabolites: No alert found
Selection: Substances different from target are removed
Sub-category: 124 chemicals with 182 experimental data

- Step 5:

Profiler: Protein binding alerts for skin sensitization by OASIS combined with Skin metabolism simulator
Target and metabolites: No alert found
Selection: Substances different from target are removed
Sub-category: 47 chemicals with 61 experimental data

- Step 6:
Profiler: Protein binding potency GSH
Target: Not possible to classify according to these rules (GSH)
Selection: Substances different from target are removed
Sub-category: 44 chemicals with 58 experimental data

- Step 7:
Profiler: Organic functional groups, Norbert Haider (checkmol)
Target: Alcohol; Amine; Carboxylic acid; Carboxylic acid amide; Carboxylic acid derivative; Carboxylic acid sec. amide; Hydroxy compound; Primary alcohol; Tertiary aliphatic amine; Tertiary amine
Selection: Substances different from target are removed
Sub-category: 9 chemicals with 16 experimental data

- Step 8:
Profiler: Structure similarity
Target: [90%,100%]
Selection: Substances different from target are removed except [50%,60%)
Sub-category: 2 chemicals with 1 experimental data

Data gap filling:
Calculation approach: takes the highest mode value from the 1 nearest neighbours, Active descriptor: log Kow (calculated), Data usage: Maximal value

References and explanations

Database information:

- REACH Skin sensitisation database (normalised)

Profilers information:

- Protein binding potency GSH
- Protein binding alerts for skin sensitization by OASIS
- Keratinocyte gene expression
- Substance type
- US-EPA New Chemical Categories

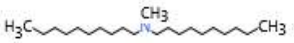
Profilers result information:

- Discrete chemical (Substance type)
- Organic (Substance type)
- Mono constituent (predefined) (Substance type)
- Aliphatic Amines (US-EPA New Chemical Categories)

Appendix: Specific report explanations

Specific information regarding the prediction

Table with profiling results for "Organic functional groups"

CAS	Structure	Results
1 CAS# No CAS number		Alcohol Amine, tertiary Carboxylic acid Organic amide and thioamide Aliphatic amine, tertiary
2 CAS# 7396-58-9		Amine, tertiary Aliphatic amine, tertiary

Structural functionalities, different from the target are colored in red.