ADMIN

MOE

EXPERT PANEL MEETING

March 13-14, 2025

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: February 14, 2025
Subject: Margin of Exposure Resource Document

Enclosed are the revised resource document on Margin of Exposure (*resource_MOE_032025*), and the transcripts from the meeting at which the document was first discussed (*transcripts_resource_MOE_032025*).

At the December 2024 meeting, the Panel discussed the varying terminology used in the systemic quantitative risk assessment (QRA) and the application of measured and realistic data versus conservative exposure parameters. The Panel requested revisions to the document to address the received comments, clarify the preferred terminology, and provide a clearer explanation of how the MOE approach should be performed in their safety evaluation process, such as the application of uncertainty factors for study duration extrapolation, avoiding over conservatism, and utilizing practice and habits data that better reflect the US consumer population.

Comments provided by the Council on the Revised Document have been carefully addressed. (*PCPCcomment_resource_MOE_032025* and *responsePCPCcomment_resource_MOE_032025*).

The Panel is requested to review the revised document and determine whether the revisions adequately represent their views on the implementation the MOE approach in systemic QRA analysis.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: November 20, 2024

SUBJECT: Draft Resource Document: Margin of Exposure (draft prepared for the December 2-3, 2024 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft resource document on Margin of Exposure.

We request that this document be issued for an official 60-day comment period before it is finalized and posted on CIR's website.

It would be helpful if the scope of the document was described at the beginning of the document. The document appears to be for systemic toxicity quantitative risk assessment (QRA) only. If this is not the objective, the document needs to be revised to include QRA for allergic contact dermatitis and local endpoints.

Rather than saying that the Expert Panel evaluates a "worst-case scenario", it would be better to state: "comparing the thresholds of toxicity to exposure estimated using maximum industry reported use concentrations by product type and often assuming complete dermal absorption as an initial approach to assess systemic exposure". Then the last sentence of the first paragraph can be deleted.

Second paragraph – Rather than "skin absorption" it would be more appropriate to state that the risk of systemic effects is influenced by the route of application. It might be inhalation for spray products and powders, oral exposure for lipsticks, and dermal exposure for many rinse-off and leave-on cosmetics.

The sub-components of the default 10X uncertainty factors for inter- and intra-species extrapolations needs to be included. Inter-species subcomponents include a 2.5X toxicokinetic factor and 4X toxicodynamic factor, while the intra-species subcomponents include a 3.2X toxicokinetic factor and a 3.2X toxicodynamic factor. This is important to establish as these defaults can be refined with data when appropriate, and/or a robust scientific rationale. Also,

there is no mention of duration extrapolation. Does the approach outlined assume the repeated dose studies are 90-days in duration?

Third paragraph – It would also be helpful to note that MOE calculations are not necessary for ingredients that are normal constituents of the body.

There is no information in the document on how the POD is selected. First the lowest human-relevant LOAEL for the endpoint of concern should be identified. Then the highest NOAEL (NOEL) below the lowest LOAEL should be used as the point of departure. The statement "(POD for the determination of an appropriate NOAEL from available data)" does not make sense as a NOAEL is usually used as a POD.

There should be additional descriptions of cosmetic habits and practices data. Generally, product use data are presented as distributions and use information at the 90-95 percentile values are used for conservative single product exposure assessments.

Because maximum use concentrations and 90-95 percentile product use values are used, adding up all product use is not recommended. For preservative cosmetic aggregate exposure, please consider using the approach outlined in the SCCS Notes of Guidance (2023 12th revision) that uses a product aggregate exposure amount of 17.4 g/day. This value assumes the preservative is used in 17 product categories.

Defaulting to 50% absorption when there are no dermal absorption data at the maximum use concentration is not always necessary. Dermal absorption data from an in vitro penetration study at a concentration different than the maximum use concentration can be used to estimate absorption. Physical chemical properties, e.g., molecular weight, ionization, log Pow, etc., must also be considered to determine if the ingredient can be considered to have very low dermal penetration. It would be helpful to cite accepted methods for estimating dermal penetration based on physical-chemical properties.

All default uncertainty factors should be explained in the same section and a table provided with those defaults. The default extrapolation from LOAEL to NOAEL is more appropriately 3X to 10X, as opposed to the 10X noted in the current document. Default duration uncertainty factors should include subacute to subchronic, and subchronic to chronic.

Route to route extrapolation needs to be explained when comparing animal studies to consumer exposure. If one corrects for dermal absorption for human exposure, one should consider correcting for oral absorption from the animal critical study, for example.

In the fifth paragraph, the POD adjusted by uncertainty factors is not used to establish an acceptable NOAEL. An adjusted POD is used to establish a safety threshold that includes corrections for uncertainty, often referred to as a reference dose.

Mention of plasma concentrations, C_{max} and AUC are not appropriate for this document unless a section on physiologically-based kinetics and how these data are used to refine default uncertainty factors is added to the document. Most cosmetic ingredients do not have this type of

data, and the factor of 25 for MOS for AUC is typically for drug development, where this type of data are more common.

It should be noted that the MOE described in this boilerplate language is for systemic toxicity only. In the boilerplate language, rather than calling an MOE a "factor", it should be called a ratio.

Instead of referencing EPA risk assessment approaches, consider referencing the National Academy of Sciences and IPCS, since EPA does not regulate cosmetics. Reference to SCCS is appropriate as written.

Before mentioning the NGRA approach, it would be helpful to mention animal testing bans for cosmetic ingredients and products around the world and including individual states in the US. References need to be provided for the NGRA approach.

The following does not belong in the last paragraph: "internal exposure level, such as plasma C_{max} could be predicted using a physiologically based kinetic (PBK) model". If this paragraph is about NGRA, the tiered approach and utilization of techniques such as TTC and SAR read-across should be discussed.

Expert Panel Resource Document: Margin of Exposure March 13-14th, 2025 Panel Meeting – Jinqiu Zhu	
Comment Submitter: Personal Care Products Council **Date of Submission: 11/20/2024**	
Comment	**Response/Action**
We request that this document be issued for an official 60-day comment period before it is finalized and posted on CIR's website.	Before finalization, the document will be made available on CIR's website for a 60-day comment period
It would be helpful if the scope of the document was described at the beginning of the document. The document appears to be for systemic toxicity quantitative risk assessment (QRA) only. If this is not the objective, the document needs to be revised to include QRA for allergic contact dermatitis and local endpoints.	The scope of this document is for systemic QRA only.
Rather than saying that the Expert Panel evaluates a "worst-case scenario", it would be better to state: "comparing the thresholds of toxicity to exposure estimated using maximum industry reported use concentrations by product type and often assuming complete dermal absorption as an initial approach to assess systemic exposure". Then the last sentence of the first paragraph can be deleted.	Revised accordingly
Second paragraph – Rather than "skin absorption" it would be more appropriate to state that the risk of systemic effects is influenced by the route of application. It might be inhalation for spray products and powders, oral exposure for lipsticks, and dermal exposure for many rinse-off and leave-on cosmetics.	Revised accordingly
The sub-components of the default 10X uncertainty factors for inter- and intra-species extrapolations needs to be included. Inter-species subcomponents include a 2.5X toxicokinetic factor and 4X toxicodynamic factor, while the intra-species subcomponents include a 3.2X toxicokinetic factor and a 3.2X toxicodynamic factor. This is important to establish as these defaults can be refined with data when appropriate, and/or a robust scientific rationale. Also, there is no mention of duration extrapolation. Does the approach outlined assume the repeated dose studies are 90-days in duration?	Addressed. The sub-components of the default 10X uncertainty factors have been included. Repeated dose studies can be either subacute (28-d), subchronic (90-d) or chronic study. If a subacute study is used, an additional uncertainty factor may be applied for extrapolation.
Third paragraph – It would also be helpful to note that MOE calculations are not necessary for ingredients that are normal constituents of the body.	It has been highlighted that QRAs should be completed on a case-by-case basis.
There is no information in the document on how the POD is selected. First the lowest human relevant LOAEL for the endpoint of concern should be identified. Then the highest NOAEL (NOEL) below the lowest LOAEL should be used as the point of departure. The statement "(POD for the determination of an appropriate NOAEL from available data)" does not make sense as a NOAEL is usually used as a POD.	Revised accordingly
There should be additional descriptions of cosmetic habits and practices data. Generally, product use data are presented as distributions and use information at the 90-95 percentile values are used for conservative single product exposure assessments.	Revised accordingly
Because maximum use concentrations and 90-95 percentile product use values are used, adding up all product use is not recommended. For preservative cosmetic aggregate exposure, please consider using the approach outlined in the SCCS Notes of Guidance (2023 12th revision)	The aggregate exposure would be addressed separately, but not in this document.

that uses a product aggregate exposure amount of 17.4 g/day. This value assumes the preservative is used in 17 product categories.	
Defaulting to 50% absorption when there are no dermal absorption data at the maximum use concentration is not always necessary. Dermal absorption data from an in vitro penetration study at a concentration different than the maximum use concentration can be used to estimate absorption. Physical chemical properties, e.g., molecular weight, ionization, log Pow, etc., must also be considered to determine if the ingredient can be considered to have very low dermal penetration. It would be helpful to cite accepted methods for estimating dermal penetration based on physical-chemical properties.	Addressed.
All default uncertainty factors should be explained in the same section and a table provided with those defaults. The default extrapolation from LOAEL to NOAEL is more appropriately 3X to 10X, as opposed to the 10X noted in the current document. Default duration uncertainty factors should include subacute to subchronic, and subchronic to chronic.	Addressed.
Route to route extrapolation needs to be explained when comparing animal studies to consumer exposure. If one corrects for dermal absorption for human exposure, one should consider correcting for oral absorption from the animal critical study, for example.	Addressed.
In the fifth paragraph, the POD adjusted by uncertainty factors is not used to establish an acceptable NOAEL. An adjusted POD is used to establish a safety threshold that includes corrections for uncertainty, often referred to as a reference dose.	Addressed.
Mention of plasma concentrations, Cmax and AUC are not appropriate for this document unless a section on physiologically-based kinetics and how these data are used to refine default uncertainty factors is added to the document. Most cosmetic ingredients do not have this type of 3 data, and the factor of 25 for MOS for AUC is typically for drug development, where this type of data are more common.	The relevant content has been deleted.
It should be noted that the MOE described in this boilerplate language is for systemic toxicity only. In the boilerplate language, rather than calling an MOE a “factor”, it should be called a ratio.	Addressed.
Instead of referencing EPA risk assessment approaches, consider referencing the National Academy of Sciences and IPCS, since EPA does not regulate cosmetics. Reference to SCCS is appropriate as written.	Some exposure factors such as surface area data are from EPA’s documents. Sometimes, the Reference Dose (RfD) or/Reference Concentration (RfC) determined by EPA may be used as the POD for MOS calculation.
Before mentioning the NGRA approach, it would be helpful to mention animal testing bans for cosmetic ingredients and products around the world and including individual states in the US. References need to be provided for the NGRA approach.	The description of NGRA has been deleted upon the Panel’s discussion.
The following does not belong in the last paragraph: “internal exposure level, such as plasma Cmax could be predicted using a physiologically based kinetic (PBK) model”. If this paragraph is about NGRA, the tiered approach and utilization of techniques such as TTC and SAR readacross should be discussed.	This paragraph has been deleted upon the Panel’s discussion.

DECEMBER 2-3, 2024 EXPERT PANEL MEETING

Belsito Team Meeting - December 2, 2024

DR. BELSITO: So, we'll move onto the margin of exposure resource paper. That's under admin. And, again, we've got a volume -- a Wave 2 rather from PCPC and I want to hear particularly Curt's comments on their comments. Do we agree with them, not agree with them?

DR. KLAASSEN: Well, I'll discuss my points here which somewhat overlap -- not totally. Okay, if we go to the third paragraph that starts out with, "human exposure is assessed," and the last line or two it says, "In the absence of sufficient durable absorption default value of 50 percent should be applied."

DR. BELSITO: What PDF are you on, Curt, or where in the document.

DR. HELDRETH: Four.

DR. KLAASSEN: It's on that first real page of the document.

DR. BELSITO: Okay, yeah. The next to the last paragraph.

DR. KLAASSEN: Right.

DR. BELSITO: Yeah.

DR. KLAASSEN: In the absence of sufficient dermal absorption data my personal opinion is that if we don't have sufficient dermal absorption, we shouldn't try to calculate a margin of exposure, but we should ask the suppliers to do that experiment. It's not a difficult experiment to do and in essence, we don't know the dose and without knowing the dose you can't do a margin of exposure. So, we should get the data. So that's number one.

DR. BELSITO: Okay, can I just comment on that? Why 50 percent? Some groups use a hundred percent as a worst-case scenario. Where does 50 percent come from?

DR. KLAASSEN: Well, yeah, you're right. A hundred percent would be the worst-case scenario. How this is largely come about is this is policy, it's not science. So, the worst-case scenario is a hundred percent. The best-case scenario is zero percent. So, some people have said let's do it halfway in between. Now, if you're with the EPA they have to come up with a number. EPA and FDA is different.

So, EPA has to come up with a number even if there's no science associated with it because that's just the way it is. But with the FDA you typically ask for the data and all we're asking for is doing some kind of an absorption study to see if it's three percent, two percent, or six percent. And I say basically the same as Dan Liebler said, if we don't know the chemistry of the compound it's dead. I'm saying if we don't know the dose, it's dead. We ask for that data.

DR. BELSITO: So, Curt, say we don't have dermal absorption but let's be ultra conservative, if we run a margin of safety and assume a hundred percent and it still gives us a sufficient margin of safety, why do we need to ask for dermal absorption?

DR. KLAASSEN: Well, I just think it's somewhat similar as with Dan Liebler's argument. If you don't know the chemistry of the compound, you don't do a study. I mean, there's just a minimum amount of data that we had, and I would say that if you don't know the dose -- what is the one line of toxicology if you boil it down to one sentence, the dose makes the poison. And if we don't know the dose, I mean, come on. We've got to have this somewhat look like it's science. Now, to figure out that dose, if it took a hundred thousand dollars to figure it out that would be a different thing, but to figure out the absorption is not an expensive experiment.

We just got to know the dose. So that's my point here.

DR. BELSITO: Paul, Allan, what are your thoughts on this?

DR. RETTIE: I can't disagree with Curt there. Toxicology is all about the dose.

DR. BELSITO: But if your hundred percent dose is fine, do we really care what the dose is? Our goal is to rely on safety, right?

DR. RETTIE: So, your question is why can't we just use the hundred percent, put it in there and call it good? I cannot really disagree with that but it's just annoying that we don't get the actual experimental data when it is pretty straightforward to do. You don't even need to do radio activity. I guess.

DR. SNYDER: I somewhat agree with Don. I mean, our default is if you don't provide us the data, we're going to assume a hundred percent absorption. I don't see any problem with that strategy as long as we're consistent in applying that strategy.

DR. KLAASSEN: What do you think about the strategies that we don't need to know the structure of the chemical? We can take the bottle of this stuff and pour it on your skin, and you don't die. We don't know what's in that bottle but that's good enough.

DR. BELSITO: That's sort of a reductio ad absurdum argument, but.

DR. KLAASSEN: It's the same thing.

DR. BELSITO: I don't know if it's the same thing.

DR. KLAASSEN: I mean, if we are going to call ourselves a scientific organization, we have to have a minimum level of science and to know the structure of a chemical and the dose is not asking too much. I mean, this is 2024.

DR. BELSITO: Not for much longer.

DR. HELDRETH: Carol has her hand up.

DR. EISENMANN: I also think you should take the physical/chemical properties of the material you're reviewing under consideration too, because if you have a polymer and it's really large, assuming a hundred percent is not appropriate either. Or if you have a charge ingredient. Yes, for some things a hundred -- but, I think you need to put in some additional verbiage in there that you can also consider physical/chemical properties because there are things you can use physical/chemical properties to predict dermal penetration. So, you should have something like that in there.

DR. KLAASSEN: Okay, so that was one issue. Another issue is throughout this document -- well, let's go down to the next paragraph and go over the fourth line. UF of ten is typically applied. I would say three to ten and that depends on the quality of the data. In fact, the last meeting that we had we use an uncertainty factor of three. I would change that three - ten and one can look at the data and decide if you want to use a three or a ten.

These are uncertainty factors so that's what I would say. If we go to the next page, the top paragraph is when the PoD, I would say that that paragraph can be eliminated. So, the EPA comes out with what they call an RFD and if the FDA comes out with another number daily acceptable dose or whatever, and so these are not points of departure. This is after the EPA and/or the FDA have already divided it by a hundred. So, I mean, I just don't see any reason to include that in there.

I think throughout here we use maybe the PoD, point of departure. We probably should be using the NOAEL because it's usually the NOAEL that we're talking about and how we come up and you use the point of departure to come up with the NOAEL, but I would use the word NOAEL.

DR. BELSITO: But the point of departure could be a LOAEL adjusted, right? I mean, the point of departure is the number you're taking where you don't expect to see an adverse event and sometimes all we have is a LOAEL which is adjusted to give us the point of departure.

DR. KLAASSEN: That was actually divided to give us a NOAEL.

DR. BELSITO: Right.

DR. KLAASSEN: Right. And I mean, this isn't a big deal, but I just think it's more appropriate to call this the NOAEL rather than the point of departure.

DR. BELSITO: Except, to me, a NOAEL is something that you actually have an experiment that has shown a level where there's no effect, whereas a point of departure can be you have an experiment that's shown a LOAEL, you don't have a NOAEL and so you adjust it for a point of departure.

DR. KLAASSEN: Well, we divide it as it said in that first line in the bottom of that paragraph is we use an uncertainty factor of three or ten. That's what that paragraph is about.

DR. BELSITO: Right.

DR. HELDRETH: We also talk in that paragraph about a subchronic NOAEL or chronic NOAEL. So, if we're just going to say NOAEL, which one are we talking about?

DR. KLAASSEN: Okay, that I would like to change also. A NOAEL -- this sounds like we use a chronic NOAEL and usually a repeated dose, it's usually a 90-day repeated dose not a two-year repeated dose. And we don't talk about for getting to a NOAEL it's from a 90-day, not from a two-year. Most chemicals, we don't have a two-year. We only have a two year if we have a carcinogenic study, right? And for how many cosmetics do we have a carcinogenic study? One out of ten probably.

DR. BELSITO: Probably not that many.

DR. KLAASSEN: Yeah. So, we use a 90-day repeated dose study. Now, the last thing I don't like, but I don't think you people agree with me on this, is that we use the 60 kilogram is what the average American weighs and so I did some research on that and the average male in the United States weighs 91 kilograms and the average female used is 77 kilograms therefore I think this should be 80 instead of 60. And when you have data, you should use the data.

If we want an uncertainty factor then we put a bigger number in an uncertainty factor, not in the data. People in the United States do not weigh 60 kilograms. We should use 80 kilograms.

DR. RETTIE: That one kind of makes sense to me. Sixty kilograms, 132 pounds. That's just too small in 2024. Eighty kilograms.

DR. BELSITO: But isn't that conservative?

DR. KLAASSEN: You put the conservatives in the uncertainty factors. You put the science in the numbers.

DR. BELSITO: I mean, I guess my only argument there is 60 is what's been always traditionally used but --

DR. KLAASSEN: I agree. But science changes and people weigh more than they did 50 years ago.

DR. BELSITO: Paul, you're silent there.

DR. SNYDER: I've been biting my tongue. I'm with you, Don. This is the convention, 60 kilograms. And so, I think departing from that is a little bit slippery, but I understand Curt's point. But like you said, it is more conservative.

DR. KLAASSEN: That's why you have the uncertainty factors. FDA is changing their numbers for the weight of humans in some of their studies. I mean, I guess I'm a scientist and think that you should use the latest science not what we did before we knew the structure of DNA.

DR. BELSITO: That was the 1940s.

DR. KLAASSEN: No, we didn't learn the structure of DNA until the early '60s. And you know, why stick with the 1950s? Because it's tradition? That's what uncertainty factors are for. We've got a ten-fold uncertainty factor within humans and another ten to go from animals to humans. Why shouldn't we be at the head of the scientific societies and groups of going to the realistic number instead of data that's 60 years old? I don't understand.

I mean, we can do it. It's straightforward, we put in there 60 or 80 but if you teach that to students, you say, well we put 60 in there. We know it's wrong because we know people weigh 80 kilogram on the average, but we use 60. Now how do you teach that in a scientific lecture? It's all tradition. We also don't know the DNA covalently binds to DNA. That wasn't known. See what the other group says. I still say you use science when you can use science. When you don't have science, you use policy and policy is the uncertainty factors.

DR. RETTIE: Well, we have another team, and we can chat with them and see where we end up tomorrow.

MR. BJERKE: Dr. Zang has her hand up.

DR. ZANG: May I? Thank you. Dr. Klaassen you mentioned that the FDA --

DR. BELSITO: Who is this speaking? Sorry.

DR. ZANG: This is Janet Zang from FDA.

DR. BELSITO: Okay, thank you.

DR. ZANG: Dr. Klaassen you mentioned that FDA has changed the number, do you mind specify which guidance or which document that you were referring to?

DR. KLAASSEN: Yeah. Not all of the offices have it's just some of the offices and, yes, I'll try to get that information for you.

DR. ZANG: Thank you very much. Because from what I know, I used to work in food. I know that 60 kilogram it's still a standard, but I'd appreciate if you could share more information. Thank you.

DR. KLAASSEN: Will do.

DR. BELSITO: There was another comment or someone else was trying to speak? No. Okay. Any other comments on this margin of exposure paper?

DR. SNYDER: No, I agreed with a lot of the comments from the PCPC and so I think that needs to come back to us.

DR. BELSITO: Okay. So let me summarize what I have here. We agree with the PCPC Wave 2 comments. In terms of absorption, Curt feels very strongly that we shouldn't just assume 50 percent. I'm not certain that we shouldn't just assume a hundred percent and if it clears, we're fine. But Curt feels we should actually measure absorption. The uncertainty factor should be in PDF page four, three to ten based upon the quality of the data. And in terms of doing our calculations, Curt feels that we should change the average weight to 80 kilos based on his data that women are 70 and men are 90. And that's what I have. Am I missing anything? Okay.

Alex, you've been very quiet. Comments from PCPC as to where we're at? You're muted.

DR. KLAASSEN: You're muted, yeah.

MS. KOWCZ: Sorry. I've just been listening to everybody. I think it's a good suggestion to listen to what the other team has to say as well tomorrow.

DR. BELSITO: Okay.

Cohen Team Meeting - December 2, 2024

Temporarily unavailable.

Full Panel – December 3, 2024

DR. COHEN: Right. This is very early days of this document. It's a great start. The outline is very good.
They are great comments from PCPC that we agreed with.
This is still a document in progress, and there's a lot of input from David and Curt. There was some issues about point of departure, use versus exposure, the 50 percent absorption, benchmark doses. There was a lot of things that needed to be done. I know there's going to be some comments further on here, but it's still way too early for releasing it out there. David, you want to comment a little bit more? And I don't if Curt has anything he wants to add to this conversation as well.

DR. ROSS: I think Don mentioned Curt had comments, so why don't Curt go ahead.

DR. KLAASSEN: Okay. I have 5 comments, quite specific. So if we go to the document, the third -- kind of the formula right there, that would be the third paragraph, sort of. Where it says MOE --

DR. COHEN: What PDF was it? Oh, it's only one and half pages. What paragraph was it, Curt?

DR. KLAASSEN: After the second paragraph. There is that little mathematical formula. Instead of the POD, which is the point of departure, it really should be NOAEL, N-O-A-E-L. And I think the other group mentioned that as well. So that's number one.
Number 2 goes to the one, two, three, fourth paragraph. The very long paragraph. Second to the last line where it talks about, if we don't have absorption data we use a default value of 50 percent. My suggestion is, if we do not have dermal absorption data we ask for it. That's not an unreasonable thing to do. Or is it an expensive experiment for industry to do?

DR. ROSS: I like that suggestion. Curt and I chatted a bit offline about that. It's not something we often ask for and we probably should be asking for it more, so.

DR. KLAASSEN: Okay, Number 3 is the next line, the last line of that long paragraph. Where it says the 60 kilogram, which I had mentioned earlier, that we really should be using 80 kilogram. And I looked up the data on that and the average woman in the United States is 77 kilograms and the average man is 90 kilograms.

DR. COHEN: Pretty heavy.

DR. KLAASSEN: So to use 60 kilogram, I don't think is scientifically valid.

DR. ROSS: We certainly didn't have a discussion about that. I mean, Curt and I didn't talk too much about that. But, you know, I think you're right, Curt. I mean, you know, people are heavier than the 60 kilos that are used here.

I dug into some of the EPA data on this as well. I think one of the problems might be our verbiage here. You know, we say a typical human body weight of 60 kilos and that's not correct.

So maybe an alternative, rather than changing the 60, would be to change our verbiage, which would be changing it to a conservative estimate of human body weight of 60 kilos.

I mean, it just builds in more conservatism into this whole approach. And you may want that, you may not, but it's certainly more protective. So I would favor actually keeping the 60, but changing the verbiage rather than changing the 60. But we can discuss that.

DR. KLAASSEN: Well, my feeling is that when you have data, you have data. And where you don't have data you use an uncertainty factor and that is really policy.
And so, we are using a 100 safety factor in essence already, so where we have data we should use data. If we don't have data we can use policy. That's my two cents.

DR. ROSS: Yeah, it's a lot. I'll just add that on the 60 kilos if you look at the EPA weight tables for women, 60 kilos is about the 20:25 percentile for females greater than 30.

And Curt's right. Certainly, the typical male, and certainly the typical female is heavier than 60. But if you want to be more conservative and protective, it's not a bad way to go. But it's certainly not a typical human body weight.

DR. BELSITO: But then we're assuming that only adults are using the product.

DR. COHEN: That's right.

DR. BELSITO: So are we going to scale this down for products that are used for babies and use a different margin of safety?

DR. KLAASSEN: Yeah. So maybe we probably should use 3 kilograms?
DR. COHEN: No, no. But, Curt, 25 percent of the population is under 18. A quarter of the population is under 18, and that population is not 80 kilos on average.

DR. ROSS: If I can just comment that the EPA has very detailed weight data to use for children. You know, really all the way up from 1 to 18. And so, you do have that data available to you if you want to use it.

You know, my other recommendation here, actually, on this document was that I felt that we needed to delete this whole sentence. Because I didn't think we needed to be that detailed. But it doesn't get around the issue of which weight to use in these calculations. Curt's proposing 80; I guess I would prefer to stick with 60, but that's where we are.

DR. KLAASSEN: Okay. Let's go to Number 4 on my list. And it's the next paragraph. Again, the second word should not be POD, but should be NOAEL. But then if we go down to the 4th line, an uncertainty factor of 10, they had, I would prefer to have 3-10. In fact at our last meeting we used an uncertainty factor of 3. And I think that gives us a little flexibility on the strength of the data that we have.

DR. ROSS: Yeah, we agree on that one. Yeah, that's absolute, yeah.

DR. KLAASSEN: If we go to the next paragraph Number -- which is my last real comment, Number 5. That whole paragraph should go. What it's talking about here, basically, is the EPA calculates an RFD, a reference dose, and the

FDA usually calculates daily acceptable intake. And those aren't PODs and those aren't -- they have put in their hundredfold safe factors already. I don't even think we need to have this paragraph here because we don't do that.

DR. ROSS: Yeah, I had it down for rewriting. It needed work. Whether it's deleted or it needs work, I think -- anyway, it needs to be changed, yeah. No question, yeah.

DR. BERGFELD: That include the formula underneath it?

DR. ROSS: Yeah. I mean, there needs to be some sort of discussion of benchmark doses. You know, EPA benchmark doses in here and ADIs. And so, I think that needs to be in here. You would need some form of formula, but probably that needs to be modified slightly.

But I think you could integrate it with the previous paragraph in a much more effective way. And Jinqiu and I chatted about that already. You know, it just needs reworking and then the Panel needs to see it again.

DR. BERGFELD: Is that your 5th?

DR. KLAASSEN: That's my fifth and last comment.

DR. BERGFELD: Last comment? How about a summary comment? Needs to be redone?

DR. ROSS: Yeah.

DR. KLAASSEN: Yeah.

DR. COHEN: A lot of editing it sounds.

DR. BERGFELD: And the rest of the paragraphs underneath are Okay? Under the formula?

DR. ROSS: The last paragraph I thought could probably go or certainly needed to be rewritten. Yeah, I'm not sure we needed that.

DR. BERGFELD: And you'll be working with Jinqiu to do that?

DR. ROSS: I'm very happy to work with Jinqiu if people want -- and Curt -- if people want us to do that.

DR. BERGFELD: Yes, let's have you do that. Okay. So is that all of the comments for this Moe resource document?

DR. BELSITO: I.
I actually disagreed with Curt about NOAEL and point of departure because we don't always have a NOAEL. Sometimes you have a LOAEL and then we adjust that and that's the point of departure. I mean the point of departure is that the level you're going to use that you consider safe.

DR. ROSS: I agree with that.

DR. BELSITO: And we don't always have a NOAEL.

DR. KLAASSEN: Okay. It's true you have different data. But the original formula is a NOAEL. Now, if you don't have a NOAEL then you can use --

DR. ROSS: A LOAEL.

DR. KLAASSEN: A LOAEL. Then if you don't have that, then one often uses the benchmark dose, and that's a mathematical way. And then, okay, we have this POD. So that's kind of maybe a third way, or 4th or 5th way, of guessing about where there is no adverse effect level.

There's no mathematical way of determining really what the POD is. What's actually considered the best is the benchmark dose.

But again, going back the way this is -- you know what? Where most of this stuff was originally described was by the National Academy of Science. Okay, that is the number one organization for science in the United States. And they use NOAEL is what we hope to have. And then we go from that. But you don't start with a point of departure, you start with a NOAEL.

DR. ROSS: Yeah, but you develop the POD, the point of departure. And it really should be POD sys, systemic point of departure. You develop that from the NOAEL or the LOAEL, So I agree with Don's point here.

DR. KLAASSEN: With what?

DR. ROSS: With respect to the first paragraph. That equation, it really still should be the POD, I think, because you can get to the POD from not just the NOAEL --

DR. KLAASSEN: No, no, no. No, no, no, no, no, no, no.

DR. ROSS: Well, you can. You can get there from a LOAEL, right, Curt? And if you look --

DR. KLAASSEN: The number one thing you try to have is a NOAEL.

DR. ROSS: Yeah. No, absolutely.

DR. KLAASSEN: If you can't get that, what do you do?

DR. ROSS: Well, then you may go to other things, but you know you generally look for -- you generally look for a NOAEL and a 90 day animal study or a reproductive toxicity study.

DR. KLAASSEN: Yeah.

DR. ROSS: They're the two things that you'll use to get a NOAEL. And so, then your MOE -- I mean all the MOEs we've generated have been from NOAELs. I agree with you there, so we've been using NOAELs.

DR. KLAASSEN: So why don't we want to use NOAEL here?

DR. ROSS: Because it's possible, it's theoretical that you can get it from another spot. You can get it from a LOAEL.

DR. KLAASSEN: Yes, but where do you start?

DR. BELSITO: Use it if it's available, Curt.

DR. KLAASSEN: Where do you start? Where do you start?

DR. BELSITO: But point of departure is a generic term.

DR. KLAASSEN: You just told us you use a NOAEL. What does the National Academy of Science say? Why are we making up this MOE business? Or not MOE, but the POD. Where is this coming from?

DR. BELSITO: It's a generic term for the level that you're going to use to say safe.

DR. KLAASSEN: Yeah, it's a generic term, I agree. We should use scientific terms as described by the National Academy of Science.

DR. BELSITO: But the NOAEL is not always available. And when you're calculating --

DR. KLAASSEN: No, I know that, neither is POD. You first do a NOAEL. And if that doesn't work -- you can even write this in here. If you don't have -- in fact, it even says in here, if you don't have a NOAEL you can take the lowest adverse effect and divide it. Right? That's where you start.
DR. ROSS: Yeah.

DR. KLAASSEN: I mean, if you ever looked at a scientific textbook about these things.

DR. ROSS: Yeah.

DR. KLAASSEN: So we're going to do something different than what all students are taught? What they have their exam on, on the DABT? I mean, why are we recreating the wheel and calling the wheel an airplane?

DR. ROSS: I don't think you're doing that, honestly.

DR. KLAASSEN: Yes, we are doing that. The NOAEL, you can look any place. That's scientifically sound and the formula for getting a margin of exposure is the NOAEL divided by the human SED, right?

DR. ROSS: I think we say that, it's typically the NOAEL generated from an animal study, right, and divided by that.

DR. KLAASSEN: Okay, you say that's typically done, but the equation that we have doesn't say that.

DR. COHEN: So is there an objection to putting the NOAEL into the equation, and then below that paragraph saying when NOAELs are not available, we could use a LOAEL?

DR. KLAASSEN: Of course.

DR. ROSS: You could probably have Jinqiu look at sort of harmonize best practices for this. I mean, I'd like our document to reflect --

DR. KLAASSEN: But our best practices never looked at the world's textbooks, nor do they look at the National Academy of Science.

DR. BERGFELD: Well, I think that Jinqiu can take a look at those references and develop an editorial change here for us to look at next time. I think that there's merit to all of the comments, but I think that we have to take seriously what Curt has said.

DR. KLAASSEN: Right. It's easy to change.

DR. ZHU: Sure.

DR. ROSS: Wilma, if I could just comment right at the bottom paragraph, and it it's derived from what Curt is discussing here so it's reasonable to point out here. And I think PCPC had a comment on it.

DR. BERGFELD: Okay, Okay.

DR. ROSS: You don't adjust the POD by uncertainty factors to get the NOAEL. That's not correct. So that needs to go. But it gets at this whole POD and NOAEL thing. And really I don't see it -- I mean, it's a major point of Curt's here and we should address it. But I don't see it as a major issue because we typically use 90-day NOAELs in our MOE derivations.

And I think Don is correct, you can get to this point of departure from other sources within the NOAEL. We typically do not do that, but it's possible, such as the LOAEL. And that's why we had this additional value, the POD, which you can get to from other ways than the NOAEL. I would say 99 percent of the time you're using NOAEL, so.

DR. KLAASSEN: But in the equation where we don't use the NOAEL, it doesn't make sense, does it? You just said that 99 percent of the time we use NOAEL, but in our equation, we're going to put POD.

DR. ROSS: But, Curt, we define it above that, that the MOE takes the no observe effect level as the point of departure. I mean, it's defined there.

DR. KLAASSEN: Where do you see that sentence?

DR. ROSS: It's the first sentence in the paragraph above there. For cosmetic ingredients, the risk of systemic effects is primarily influenced by skin absorption. MOE takes the NOAEL from an animal study -- and that should be a 90-day chronic dosing animal study or reproductive study -- as the point of departure and typically etcetera, etcetera, etcetera. So we define it as typically using a NOAEL. So, I don't really see it as such a major point as you do, but.

DR. KLAASSEN: I just say that we should have the NOAEL instead of the POD. Why don't we have benchmark dose?
That's much better.

DR. ROSS: Because we addressed it with -- .

DR. KLAASSEN: Benchmark dose is much better than a POD. Why don't we use that?

DR. ROSS: Yeah, you can get to these point of departures from numbers of different ways, right? So whether it's a LOAEL, or whether it's a benchmark dose, or whether it's a NOAEL, I think that was Don's point.

DR. KLAASSEN: I agree, but you start out, as you said, 99 percent of the time with NOAEL. So in the equation you write NOAEL.

DR. ROSS: What about when you want to use a benchmark dose or a LOAEL?

DR. KLAASSEN: You can describe that, wright about it.

DR. BERGFELD: I think that we can accommodate both opinions here.

DR. KLAASSEN: We can rewrite this so easy.

DR. BERGFELD: I think that we will assign Jinqiu to do that. I think that you've heard the comments on both sides and I think a further explanation and definitions are in order here. So I'm going to call the end to the comments and say we'll look at this next time again and see if we can't agree with what has been said and written.

DR. BELSITO: Can I interject one comment though? I think that as a Tier 1 -- now Curt thinks we should ask for absorption regardless of whether we can clear it.
But I think as a Tier 1, if we're looking at a conservative approach we should assume 100 percent absorption, not 50. That has been typically what I've been used to using on other Panels. I don't know why -- I mean -- curt says, yeah, well the max is 100, the min is 0 and so 50 is in between. But I would prefer a conservative approach for absorption to be 100, not 50.

DR. BERGFELD: Is everybody agreeable to that?

DR. KLAASSEN: No.

DR. ROSS: I was just going to comment where the 50 came from. It came from the SCCS Notes of Guidance. That's the guidance in that document, and that's where the 50 percent comes from.
I agree. Don, if you want to use 100 percent you can do that as a Tier 1. And if you clear it on the Tier 1 than you're golden, right, because you don't have to do anything else. Yeah, I think you could certainly look at that.

DR. BERGFELD: Curt, did you want to make a remark?

DR. KLAASSEN: It's not science. And if you can ask the people -- if you can ask the manufacturers for that data, which is so easily to come by, we should ask for it. Just like Dan Liebler said, there was a red line in the sand, that you have to give me the chemical that's in the ingredient. If you don't give me the chemical, then we don't do a safety assessment. I'm saying that from the biology standpoint, we have to know the absorption.

DR. ROSS: I actually like Curt's point here. You know, requesting the absorption is a good thing, I think, if we haven't got it. And then the PCPC also had some good comments, that using the bracketed percent absorption closest to what we do have. And we can do that also.

DR. BERGFELD: Okay. All right. I think that we've discussed this to a good end. And we need to see the document, again, that Jinqiu comes up with after all this discussion. So. I'm going to call an end to this discussion for the MOE for this time. This is a working document; we're not going to go live for a while. So we're really comfortable with what has been said and the directions given.

So we come to the end of all the ingredients and the resource documents that we had to review for today. And just to say we are live next meeting, which is March 13th and 14th, and it will be at the Marriott Georgetown Hotel in DC. I want to wish you all a happy holiday, Merry Christmas, those who do celebrate that. And, Bart, is there something that you'd like to say in closing?

DR. HELDRETH: Just thank you all very much for doing all of this hard work. It's a lot to wrap your head around and yet not get yourself wrapped around the axle as Dr. Cohen likes to say. And you all did it. So thank you so much and as Dr. Bergfeld said, happy holidays and looking forward to see you in the spring.

DR. COHEN: Bye everyone.

DR. BERGFELD: Bye everyone. Thank you all.

DR. BELSITO: Take care, bye bye.

DR. KOWCZ: Bye, everybody. Thank you, everyone.

MS. FIUME: Bye everyone. Happy holidays.

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

Draft Resource Document

Margin of Exposure

03/2025

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This resource document was prepared by Jinqiu Zhu, Ph.D., D.A.B.T., E.R.T., D.C.S.T., CIR Toxicologist.

555 13th Street, NW, Suite 300W, Washington, DC 20004
(email) cirinfo@cir-safety.org (CIR website) https://www.cir-safety.org
(Panel website) https://ingredientsafetyexpertpanel.org

ABBREVIATIONS

ADI	acceptable daily intake
BMD	benchmark dose
DART	developmental and reproductive toxicity
EPA	Environmental Protection Agency
EU	European Commission
LOAEL	lowest-observed-adverse-effect-level
MOE	margin of exposure
MOS	margin of safety
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
Panel	Expert Panel for Cosmetic Ingredient Safety
PCPC	Personal Care Products Council
POD	point of departure
QRA	quantitative risk assessment
RfD	reference dose
SCCS	Scientific Committee on Consumer Safety
SED	systemic exposure dose
UF	uncertainty factor

The Expert Panel for Cosmetic Ingredient Safety (Panel) adopts a risk-based approach for safety assessments by comparing the thresholds of toxicity to exposure estimated using maximum industry reported use concentrations by product type, and often assuming complete dermal absorption as an initial approach to assess systemic exposure. When appropriate, this strategy employs the quantitative risk assessment (QRA) technique that prominently incorporates the calculation of the Margin of Exposure (MOE).

For cosmetic ingredients, the risk of systemic effects is influenced by the route of application, which varies depending on the product type. Given the intended use of the product, all potential routes of exposure, including dermal, oral, and inhalation, should be considered, such as dermal exposure for rinse-off and leave-on cosmetics, oral exposure for lipsticks, and inhalation exposure for products used in spray applications or in power form. For cosmetics, the MOE typically takes the no-observed-adverse-effect-level (NOAEL) from an animal study as point of departure (POD),[1] and the systemic exposure dose (SED) for dermal application under intended use conditions is derived as the exposure estimate. Data from a repeated-dose toxicity study in animals with oral administration is used as a surrogate for dermal exposure. Typically, an MOE should be 100 or greater to indicate safety. This value of 100 incorporates extrapolation factors of 10X each for both inter- and intra-species differences. Inter-species subcomponents include a 2.5X toxicodynamic factor and 4X toxicokinetic factor, while the intra-species subcomponents include a 3.2X toxicokinetic factor and a 3.2X toxicodynamic factor.

MOE = NOAEL*/Human SED

* The NOAEL refers to the highest dose of a cosmetic ingredient administered to laboratory animals over a 90-d period or in developmental and reproductive toxicity (DART) studies that does not result in any adverse effects. If a NOAEL is not available, the lowest-adverse-effect-level (LOAEL) from a 90-d repeated-dose study or DART study in laboratory animals, divided by an Uncertainty Factor (UF) of 3 or 10–depending on the quality of the study–can be used as a substitute for the NOAEL. Additionally, the Benchmark Dose (BMD), which is mathematically derived by incorporating all data from the 90-d repeated-dose study and DART study, and extrapolating to a 10% response level, may also be used in safety calculations as an alternative to the NOAEL.

QRAs should be completed on a case-by-case basis. In the case where a cosmetic ingredient has poor bioavailability (e.g., very low dermal absorption), systemic exposure may be negligible, and an MOE calculation might not be necessary. The POD is typically determined through a structured process to ensure scientific reliability. Initially, the LOAEL is identified from the most relevant study in terms of quality, duration of exposure and key toxicity endpoints. Then, the highest NOAEL or no-observed-effect-level (NOEL) below the lowest LOAEL is selected as the POD. Upon completion, the QRA should be based on a specific endpoint of concern that has been identified for that ingredient, and should be protective for other endpoints of concern.

Human exposure is assessed for both systemic and dermal effects based on the uses of an ingredient in cosmetic products. Exposure assessments should clearly distinguish between exposure from the ingredient itself and from the product. This involves considering the concentration of the ingredients in respective cosmetic product categories and conditions of use. In addition, exposure estimates should consider high exposure products, such as products intended to be used on a large surface area of the body, and not just the products with the highest reported use concentrations. Data on practices and habits, when presented as distributions, allow for a conservative exposure assessment of individual products by utilizing values from the 90^{th} to 95^{th} percentiles. Exposure parameters can be determined using a wide variety of data sources, including the Personal Care Product Council (PCPC) habits and practices data,[2-4] which reflect usage patterns in the U.S. Additionally, guidance documents and published literature provide relevant data for exposure estimations in Europe, Asia, and other global regions.[5-21] It is essential that the descriptions clearly explain what the values used in the exposure assessment represent. The most accurate use data and exposure models coupled with appropriate endpoints of concern should be used in MOE calculations. Use data from the US should be prioritized if available. When actual exposure measurements under in-use conditions are available in the literature, the measured values should be used rather than estimated values.

To ensure conservative exposure estimates, the maximum use concentration of the ingredient in product categories, as reported by PCPC surveys, is used in the calculation of the SED. If appropriate dermal absorption data are not available, it should be requested. Alternatively, if dermal absorption data are available but only use a

higher concentration of material than the maximal use concentration, it may be used. The SED is the dose of a cosmetic ingredient that is absorbed via the skin or other exposure routes and enters the systemic bloodstream of humans. This data is most often obtained by an in vitro study where the amount of the ingredient that passes through a small patch of skin is quantified, and then extrapolated to the area of skin to which the ingredient will be delivered. An in vivo method is to use a radioactive-labeled ingredient and then quantify its excretion in the urine and feces. Physical and chemical properties such as molecular weight, ionization, and log Pow may also be evaluated to assess dermal penetration. For instance, cosmetic ingredients characterized by certain physicochemical properties–molecular weight > 500 Da, a high degree of ionization, a log P_{ow} of $\leq$ -1 or $\geq$ 4, a topological polar surface area > 120 $Å^2$, and a melting point > 200°C–may indicate very low dermal absorption.[22] In the absence of any dermal absorption data, default values of 50% absorption (SCCS Notes of Guidance)[10] or 100% absorption as Tier 1 approaches may be applied. A value of 60 kg is used for adult weight which adds another layer of conservatism in the MOE calculation. For non-adults, the weight parameter is adjusted according to Environmental Protection Agency (EPA) guidelines.[23]

To account for potential differences between the experimental setting and the actual human exposure scenarios, UFs can be utilized for study duration extrapolations. When a NOAEL is not available, an UF of 3X to 10X is commonly applied to the LOAEL to derive the NOAEL.[24,25] For converting a subchronic NOAEL to a chronic NOAEL, an UF of 10X is typically applied. Route-to-route extrapolation of toxicity should be conducted on a case-by-case basis, as it requires evaluating substance-specific toxicokinetic and toxicodynamic profiles across different exposure routes and is based on equivalent internal rather than external dose to assess safety. When comparing animal studies to consumer exposure, for example, it may be necessary to adjust for dermal absorption in humans and consider correcting for oral absorption from a relevant critical animal study.

If a regulatory Reference Dose (RfD) or Acceptable Daily Intake (ADI) value is available, a Margin of Safety (MOS) can be calculated by dividing the RfD or ADI by the estimated human exposure. As UFs are already built into these terms, an MOS value of > 1 is considered to indicate safety. While in scientific literature the terms MOE and MOS are often used interchangeably, the Expert Panel considers these as two different concepts.

The Panel considers including boilerplate language in reports when a systemic QRA approach is applied:

"Margin of exposure (MOE) is a quantitative ratio calculated for cosmetic ingredients by dividing the NOAEL obtained for an ingredient in an animal experiment by the estimated systemic exposure dose (SED) for the ingredient in humans, generally according to US EPA and European Commission (EC) Scientific Committee on Consumer Safety (SCCS) guidelines. An MOE value greater than 100 has traditionally been considered an indication of safety. The basis for this MOE value of 100 comes from two multiplication factors: a 10-fold factor for extrapolating data from test animals to human being (interspecies extrapolation), and an additional 10-fold for differences among the human population (intraspecies extrapolation). Notably, the MOE value is sometimes referred to as the margin of safety (MOS) despite the parameters being definitionally different."

REFERENCES

1. Committee to Review the IRIS Process, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process. Chapter 7: Derivation of Toxicity Values. . 2014.

2. Loretz LJ, Api AM, Barraj LM, et al. Exposure data for cosmetic products: lipstick, body lotion, and face cream. *Food Chem Toxicol*. 2005;43(2):279–291. https://www.ncbi.nlm.nih.gov/pubmed/15621341.

3. Loretz LJ, Api AM, Babcock L, et al. Exposure data for cosmetic products: facial cleanser, hair conditioner, and eye shadow. *Food Chem Toxicol*. 2008;46(5):1516–1524. https://www.ncbi.nlm.nih.gov/pubmed/18243463.

4. Loretz L, Api AM, Barraj L, et al. Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. *Food Chem Toxicol*. 2006;44(12):2008–2018. https://www.ncbi.nlm.nih.gov/pubmed/16920244.

5. Hall B, Tozer S, Safford B, et al. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments. *Food Chem Toxicol*. 2007;45(11):2097–2108. https://www.ncbi.nlm.nih.gov/pubmed/17683841.

6. Hall B, Steiling W, Safford B, et al. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments Part 2. *Food Chem Toxicol*. 2011;49(2):408–422. https://www.ncbi.nlm.nih.gov/pubmed/21093525.

7. Steiling W, Buttgereit P, Hall B, et al. Skin exposure to deodorants/antiperspirants in aerosol form. *Food Chem Toxicol*. 2012;50(6):2206–2215. https://www.ncbi.nlm.nih.gov/pubmed/22450565.

8. IFRA (International Fragrance Association)-RIFM(Research Institute for Fragrance Materials). 2015IFRA RIFM QRA Information Booklet Version 7.1https://ifrafragrance.org/docs/default-source/ifra-code-of-practice-and-standards/background-scientific-information-and-guidelines/ifra-rifm-qra-information-booklet-v7-1.pdf?sfvrsn=1426bcb8_0.

9. Api AM, Basketter DA, Cadby PA, et al. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regul Toxicol Pharmacol*. 2008;52(1):3–23. https://www.ncbi.nlm.nih.gov/pubmed/18406028.

10. Scientific Committee on Consumer Safety. 2023. The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation, 12th Revision. https://health.ec.europa.eu/latest-updates/sccs-notes-guidance-testing-cosmetic-ingredients-and-their-safety-evaluation-12th-revision-2023-05-16_en. Last Updated: 2023. Date Accessed: February 8, 2024.

11. Yamaguchi M, Araki D, Kanamori T, et al. Actual consumption amount of personal care products reflecting Japanese cosmetic habits. *J Toxicol Sci*. 2017;42(6):797–814. https://www.ncbi.nlm.nih.gov/pubmed/29142178.

12. Shaaban H, Alhajri W. Usage Patterns of Cosmetic and Personal Care Products among Female Population in Saudi Arabia: Important Factors for Exposure and Risk Assessment. *J Environ Public Health*. 2020;2020:8434508. https://www.ncbi.nlm.nih.gov/pubmed/32322284.

13. Luo G, Wu Z, Xie Z. Determining the cosmetics usage patterns of consumers for exposure assessment in China. *Food Chem Toxicol*. 2025;197:115273. https://www.ncbi.nlm.nih.gov/pubmed/39863074.

14. Lee E, Yun J, Ha J, et al. Assessment of exposure for baby cosmetic care products in a Korean population. *Food Chem Toxicol*. 2017;106:107–113. https://www.ncbi.nlm.nih.gov/pubmed/28549762.

15. Juraimi SA, O'Brien J, Hirsh J, et al. Consumer habits and practices for cosmetics and personal care products in Singapore: An online survey. *Food Chem Toxicol*. 2023;174:113659. https://www.ncbi.nlm.nih.gov/pubmed/36791904.

16. Jung K, Choi M, Hong S, et al. Realistic and aggregated exposure assessment of Korean men and women to color make-up products. *Food Chem Toxicol*. 2018;118:382–389. https://www.ncbi.nlm.nih.gov/pubmed/29758314.

17. Ficheux AS, Morisset T, Chevillotte G, Postic C, Roudot AC. Probabilistic assessment of exposure to nail cosmetics in French consumers. *Food Chem Toxicol*. 2014;66:36–43. https://www.ncbi.nlm.nih.gov/pubmed/24447976.

18. Ficheux AS, Gomez-Berrada M, Roudot AC, Ferret PJ. Consumption and exposure to finished cosmetic products: A systematic review. *Food Chem Toxicol*. 2019;124:280–299. https://www.ncbi.nlm.nih.gov/pubmed/30529261.

19. Ficheux AS, Chevillotte G, Wesolek N, et al. Consumption of cosmetic products by the French population second part: Amount data. *Food Chem Toxicol*. 2016;90:130–141. https://www.ncbi.nlm.nih.gov/pubmed/26898167.

20. Dornic N, Ficheux AS, Roudot AC. Consumption of cosmetic products by the French population. Third part: Product exposure amount. *Food Chem Toxicol*. 2017;106:209–222. https://www.ncbi.nlm.nih.gov/pubmed/28571772.

21. Biesterbos JW, Dudzina T, Delmaar CJ, et al. Usage patterns of personal care products: important factors for exposure assessment. *Food Chem Toxicol*. 2013;55:8–17. https://www.ncbi.nlm.nih.gov/pubmed/23174517.

22. Ates G, Steinmetz FP, Doktorova TY, Madden JC, Rogiers V. Linking existing in vitro dermal absorption data to physicochemical properties: Contribution to the design of a weight-of-evidence approach for the safety evaluation of cosmetic ingredients with low dermal bioavailability. *Regulatory toxicology and pharmacology : RTP*. 2016;76:74–78.

23. U.S. Environmental Protection Agency (EPA). Exposure Factors Handbook (2011 edition) Chapter 8—Body Weight Studies. https://www.epa.gov/sites/default/files/2015-09/documents/efh-chapter08.pdf.

24. US Environmental Protection Agency. 2024. Reference Dose (RfD): Description and Use in Health Risk Assessments - Background Document 1A . https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments. Last Updated: 2024. Date Accessed: September 4, 2024.

25. European Centre for Ecotoxicology and Toxicology of Chemicals . 2024. Derivation of Assessment Factors for Human Health Risk Assessment - Technical Report No. 86. https://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-086.pdf. Last Updated: 2024. Date Accessed: February 8, 2024.