Data Supplement

Memo
Use
Comments:
  Inositol
  Phenylenediamine
MOE

EXPERT PANEL MEETING
December 2-3, 2024

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, PhD, Executive Director, Cosmetic Ingredient Review
Date: November 22, 2024
Subject: Steering Committee Results and Other Communications

The CIR Steering Committee convened on November 20, 2024 to elect a new member to the Expert Panel for Cosmetic Ingredient Safety and to consider the addition of 2 proposed rereview report pathways. The Committee had a very challenging charge before them, electing just one of the 6 outstanding Expert Panel nominees. After much deliberation, **the Committee elected Dr. Samuel Cohen**, Havlik-Wall Professor of Oncology, Department of Pathology, Microbiology, and Immunology, and the Buffett Cancer Center, University of Nebraska Medical Center, to be the next addition to the Expert Panel (and fulfilling Dr. *David* Cohen's team roster). In addition to his extensive expertise in chemical carcinogenesis, risk, and safety assessments, Dr. Cohen has served on multiple panels including the FEMA Flavors Panel. He will officially begin his tenure with the Expert Panel heading into the March 2025 meeting.

The Committee considered the addition of 2 rereview report pathways for the Expert Panel's use. The first proposed addition includes the insertion of the following language into the Procedures (when considering a rereview proposal), "if the Expert Panel concludes that use in cosmetic products has been discontinued (in the US), the Expert Panel may issue a statement of its reasons and a conclusion of 'use not supported' in a Rereview Summary for publication." **Thus, for ingredients proposed for rereview, wherein use in cosmetics appears to be discontinued, the Expert Panel may choose to not re-open the report, and yet issue a Rereview Summary with a new conclusion of "use not supported."** The Committee approved of this addition, and the Expert Panel may proceed to use this pathway whenever they deem appropriate.

The 2nd pathway the Committee considered included the proposed insertion of the following language into the Procedures (also when considering a rereview proposal), "if the Expert Panel concludes, after considering any new data and information that have become available since the publication of the Final Report, that a rereview is not warranted but expanded summarization and publication of the data would be in the best interest of the public, the Expert Panel may issue a statement of reasons for that conclusion in an Expanded Re-Review Summary for publication." **This pathway is intended to provide the Expert Panel with an efficient route to publish relevant new data and other safety information, even when a report is not re-opened and the conclusion is unchanged.** The Committee also approved of this addition, and the Expert Panel may proceed to use this pathway whenever they deem it appropriate. A few other small, purely editorial, changes are to be made to the Procedures, and the updated document will be published (superseding the 2019 version) before year-end.

Also in this supplement, Monice has provided an explanation of some changes we have made in regard to detailing use; these proposed changes have been incorporated into the reports that were presented to the Panel for this meeting. Comments have also been received on the 2 Final Reports at this meeting, Inositol (from Council) and PPD (from Council and WVE), as well as on the draft MOE Resource Document (from Council). Please find all of these enclosed herein.

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice M. Fiume, M.B.A.
Senior Director, CIR
Date: November 22, 2024
Subject: Wave 2 – Use section update and present practices of use and concentration clarification paragraphs

Enclosed please find the proposed updates to the Cosmetic Use section boilerplate language, as well as wording suggested for use in the Discussion. The proposed introductory paragraph for the Use section now identifies what is meant by "present practices of use and concentration" (wording bolded for easy identification by the Panel). The fact that data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems is no longer stated in the introductory paragraph, but instead, will be explained in a separate paragraph in the Use section. These proposed changes have been incorporated into the reports that were presented to the Panel for this meeting. For comparison, the previous Use section boiler plates follow the attached proposed updates.

Also included for your review is wording proposed for inclusion in the Discussion that again verifies what is meant by "present practices of use and concentration" (once more, wording bolded for the Panel). Please consider as you review the reports during Breakout Teams.

USE

Cosmetic

(changes in this section were made prior to the Dec 2024 meeting to include reference to the RLD and to identify what "in the present practices of use and concentration" refers to)

Introductory paragraph for the Use section

The safety of the cosmetic **[**ingredient/ingredients**]** addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of **[**ingredient/family name**]** in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), **and it is these values that define the present practices of use and concentration**. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). Consequently, RLD are product-centric, whereas VCRP data were ingredient-centric. However, because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use.

[SUMMARIZATION OF USE DATA]

This paragraph is placed following the summarization of use data

Some products containing **[**ingredient/family name**]** may be marketed for use with airbrush delivery systems; however, this information is not available from the VCRP, RLD, or the Council survey. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the frequency and concentrations of use of **[**this ingredient/these ingredients**]**, and without consumer habits and practices data or particle size data related to this use technology, the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

DISCUSSION

(changes in this section were made as a result of discussions at the Sept 2024 meeting to include verification as to what "in the present practices of use and concentration" refers to)

Introductory sentence of Discussion

This assessment reviews the safety of **[**ingredient/family name**]** as used in cosmetic formulations, **in accordance with the product categories and concentrations of use identified in the Use section and Use table**. The Panel concluded **[**state conclusion**]**.

PREVIOUS VERSION

The safety of the cosmetic ingredient(s) addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of [this ingredient/these ingredients] in cosmetics, and does not cover their use in airbrush delivery systems. Data included herein were obtained from the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) in 2023 and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data were provided by cosmetic product categories, based at that time on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

[SUMMARIZATION OF USE DATA]

Although products containing [this ingredient/some of these ingredients] may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of [this ingredient/these ingredients] (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

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 19, 2024

SUBJECT: Draft Final Report: Safety Assessment of Inositol as Used in Cosmetics (draft prepared for the December 2-3, 2024 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of Inositol as Used in Cosmetics.

Introduction – In the Introduction, rather than saying "various polyol phosphates including phytic acid, sodium phytate, phytin, and trisodium inositol phosphate, which are inextricably linked to Inositol", it would be helpful to state how they are linked. For example, changing "polyol phosphates" to "inositol phosphates" would make it clearer that Inositol is a component of all the mentioned previously reviewed ingredients.

Cosmetic Use – It is misleading to call the VCRP data "ingredient-centric". The raw VCRP data is also "product-centric", it is just that FDA provided the VCRP data to CIR in a format that was "ingredient-centric". It is a difference in how the data were historically provided to CIR.

The Cosmetic Use section should also note that small businesses are exempt from MoCRA reporting for most cosmetic product categories. MoCRA defines a small business as average gross annual sales of cosmetic products in the United States for the previous 3 years of <$1,000,000 adjusted for inflation and the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 hours (see section 612 of MoCRA).

Cosmetic Use; Table 2 – The new FDA cosmetic product categories split four makeup product categories (foundations, leg and body paints, makeup bases, other makeup preparations) into traditional or airbrush use, and information on airbrush use is also requested for indoor tanning products, so some information on use in airbrush delivery systems may be available from the new FDA data. As part of the concentration of use survey, PCPC has also been asking for information on airbrush use, but so far, no such use has been reported. The airbrush information in the Cosmetic Use section needs to be revised to reflect these changes.

For Inositol, Table 2 indicates use in foundations (traditional), makeup bases (traditional) and other makeup preparations (this needs to be modified by adding traditional or airbrush). If the other makeup preparations are traditional applications, the Cosmetic Use section should note that for the makeup categories for which FDA is collecting information on airbrush uses, no airbrush uses of Inositol were reported.

Clinical, Effects Observed with Use of Inositol for Disease/Disorder Treatment – Please note the route of exposure for the studies in which Inositol was used to treat disease. Were the studies all by oral exposure?

Summary – For the oral absorption study, it would be helpful to be specific and say the species used (rats) rather than "animals".

Discussion – Please revise the following: "the 2 isomers used in the production of Inositol include myo-inositol and D-chiro-inositol". This is confusing. It should be made clear that myo-Inositol and D-chiro-Inositol are the two isomers that are reported to be used in cosmetic products.

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 19, 2024

SUBJECT: Draft Final Report: Amended Safety Assessment of p-Phenylenediamine, p-Phenylenediamine HCl, and p-Phenylenediamine Sulfate as Used in Cosmetics (draft prepared for the December 2-3, 2024 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Amended Safety Assessment of p-Phenylenediamine, p-Phenylenediamine HCl, and p-Phenylenediamine Sulfate as Used in Cosmetics.

Cosmetic Use – It is misleading to call the VCRP data "ingredient-centric". The raw VCRP data is also "product-centric", it is just that FDA provided the VCRP data in a format that was "ingredient-centric". It is a difference in how the data were historically provided to CIR.

The Cosmetic Use section should also note that small businesses are exempt from MoCRA reporting for most cosmetic product categories. MoCRA defines a small business as average gross annual sales in the United States of cosmetic products for the previous 3 years of <$1,000,000 adjusted for inflation, and the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 hours (see section 612 of MoCRA).

It should be noted that FDA is collecting data for airbrush use of four makeup product categories and indoor suntan products (none of which had uses of p-Phenylenediamine or its salts). The PCPC surveys also request that airbrush uses be identified.

It should be made clear that the limit of 2% in Europe is the "on-head" concentration limit.

ADME, In Vitro, p-Phenylenediamine – The units for MAPPD formation are stated as nmol/mg/min, while the units for DAPPD formation are stated as nmol/mg protein/min. It is likely that "protein" should also be after mg in the units for MAPPD formation.

Genotoxicity, old report summary – It is not clear what is meant by different "chemicals for

induction". The original report did use the word "induction" when describing mutation assays, but p-Phenylenediamine was tested in all the assays. Perhaps this should be something like, "different grades of p-Phenylenediamine" or "p-Phenylenediamine containing different levels of impurities".

Summary – It would be helpful to include the number (5502) of hair dye uses reported to the RLD.

Distributed for Comment Only -- Do Not Cite or Quote

WOMEN'S VOICES FOR THE EARTH

November 19, 2024

Re: Comments on the Amended Safety Assessment of p-Phenylenediamine, p-Phenylenediamine HCl, and p-Phenylenediamine Sulfate as Used in Cosmetics

To the CIR:

I am so pleased to see the RLD data being incorporated into draft safety assessments. This data gives a much more complete picture of ingredient use, than previously available, which I hope will be of use to the CIR Expert panel.

RLD Data on eye products

With respect to the PPD RLD data, it is noted that there were 51 reported uses in eyelash and eyebrow dyes. While it is made clear in the Use section, that PPD is not permitted in eye products by the FDA, there is no mention of the risks of PPD in eye products in the conclusion section. In contrast, there is a sentence in the conclusion about PPD being unsafe in temporary black henna tattoos (which are equally not permitted by the FDA, but for which the RLD data indicated zero present uses.) Given the apparent availability of eye products containing PPD, it would be useful to cosmetic users (and manufacturers) to also clearly state that PPD is unsafe in eye products in the conclusion.

Response to my comments on life-threatening adverse reactions

Also, I would like to respond to the CIR staff memo responding to my comments on PPD exposure and the potential for life-threatening adverse reactions. The CIR response noted that I asked the CIR panel to more explicitly address the case reports listed in the report. The response further stated that:

> *"… case reports should not be relied upon as test data; they serve primarily as preliminary observations that require further validation through quantitative experimental or observational study designs, such as clinical trials or cohort studies. Therefore, although the table provides the details of the case report, exhaustive descriptions are not appropriate for inclusion in the main body or the Summary section of CIR reports."*

It is worth noting that the evidence in the report on **adverse skin reactions from temporary black henna tattoos** is also entirely comprised of case reports, yet there is considerable discussion in the report of these adverse outcomes from temporary tattoos in the abstract, main body, summary, discussion and conclusion sections.

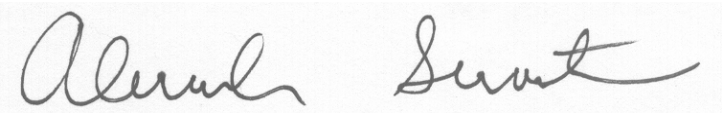
Posner Center: 1031 33rd Street, Denver, CO 80205 406.543.3747 www.womensvoices.org womensvoices@womensvoices.org

Technically if you look at the numbers, the draft report contains 13 papers discussing 27 cases of adverse reactions to hair dye in Table 12, and very similarly, 14 papers discussing 37 cases of adverse reactions to temporary tattoos in Table 13.

The rationale for discussing the tattoo reactions at length (which while certainly concerning are not life-threatening) but barely mentioning the anaphylactic shock reactions is unclear.

Further, it is worth noting, that while the general public is less likely to have read published case reports in the medical literature, they will commonly have been exposed to case reports of extreme hair dye reactions reported by their local news and through social media. I have compiled below 20 such case reports of anaphylactic reactions to hair dye reported just in the last few years. In each story, PPD allergy is mentioned as the physician's diagnosis. The stories and photos are horrifying and have been seen and remembered by millions of people across the world. While I fully understand that these news reports do not belong in the safety assessment, the Expert Panel should be aware of them. It seems appropriate for the CIR expert panel to at least discuss the similar published case reports and explain in the report how a conclusion of "safe as used" for PPD has still been justified. It would be to the detriment of the Expert Panel's reputation, to publish a report which does not appropriately acknowledge these extreme reactions to PPD that so many people relying on your judgment, are already aware of.

Thank you for your consideration of these comments.



Alexandra Scranton
Women's Voices for the Earth

News stories of extreme reactions to PPD in hair dye

I Dyed My Hair Black and It Nearly Killed Me. Oct 26, 2023

https://www.newsweek.com/woman-almost-dies-allergic-reaction-hair-dye-1837829

"My throat and tongue started swelling, and I was struggling to breathe. My friend had to call an ambulance."

DYE ANOTHER DAY My eyes swelled shut and it felt like a million ants were burrowing into my head after an allergic reaction to hair dye. Dec. 19 2019

https://www.the-sun.com/lifestyle/160070/my-eyes-swelled-shut-and-it-felt-like-a-million-ants-were-burrowing-into-my-head-after-an-allergic-reaction-to-hair-dye/

"A woman was left unable to open her eyes after an allergic reaction to hair dye caused her face to balloon and she was left with burning itching sores on her scalp for three weeks."

Woman, 20, 'nearly dies' from severe allergic reaction to hair dye. Sept. 12, 2022

https://needtoknow.co.uk/2022/09/12/woman-20-nearly-dies-from-severe-allergic-reaction-to-hair-dye/

"After transitioning from blonde to brown tresses, within four hours, Jordan started to notice a bright red, itchy swelling on her scalp. *Soon after, her entire face swelled up and her chest went tight as she was unable to drink, eat and struggled to breathe – as the young woman was rushed to hospital."*

Receptionist left 'looking like an alien' after scary allergic reaction to hair dye. Aug 11, 2021

https://www.mirror.co.uk/news/world-news/receptionist-left-looking-like-alien-24735165

"Shaylene Gartly's face swelled to three times its normal size when she treated herself to a trip to the salon last month."

Woman, 44, who was embarrassed by her grey hair reveals her face 'ballooned' to DOUBLE its size after she used £5 Schwarzkopf box dye at home. Oct. 6, 2022

https://www.dailymail.co.uk/femail/article-11286523/Woman-embarrassed-greys-reveals-Schwarzkopf-home-dye-face-DOUBLE-size.html

"A woman who was embarrassed by her grey hair has revealed how an allergic reaction to Schwarzkopf dye made her face 'balloon' to double its normal size.

Teenager, 14, who had her eyebrows tinted at salon ended up in hospital on Christmas Day - where doctors claimed allergic reaction could have left her DEAD or blind Dec. 29,2021

https://www.dailymail.co.uk/femail/article-10353069/A-girl-got-eyebrows-tinted-lost-sight-severe-allergic-reaction.html

"A teenager was left with her eyes 'glued shut' after suffering a severe allergic reaction to an eyebrow treatment at a local shop in Colchester."

Korean man's head balloons after dyeing hair in salon. Sept. 11 2016

https://stomp.straitstimes.com/singapore-seen/singapore/korean-mans-head-balloons-after-dyeing-hair-in-salon

'I ended up in hospital after using box hair dye' Aug. 14, 2024

https://www.bbc.com/news/articles/cged7442g2jo

"A man has resigned himself to "going grey gracefully" after he had an allergic reaction from hair dye which made his head "look like a balloon" on a trip to a family wedding."

TikToker Goes Viral After Face Swells from Allergic Reaction to Hair Dye: 'Really Scary to Experience'. Aug. 12, 2021

https://people.com/style/tiktoker-goes-viral-for-allergic-reaction-to-hair-dye/

"Ellison included a clip of her and a friend waiting for their hair dye to process, followed by several photos of one side of her face looking severely swollen and a video en route to the emergency room."

A Common Hair-Dye Ingredient Caused This Woman's Face To Swell Like A 'Lightbulb' Dec. 3 2018

https://nz.news.yahoo.com/common-hair-dye-ingredient-caused-154500201.html

"Estelle, a 19-year-old student, applied hair dye and immediately experienced irritation and swelling-and had to be sent to the hospital."

I turned into an 'emoji' from hair dye and I could have died. Aug. 25, 2022

https://nypost.com/2022/08/25/horrific-hair-dye-reaction-leaves-woman-looking-like-emoji/

"My scalp started burning like it was on fire and then I used a napkin and could tell my scalp was oozing," she described, adding that "as the hours went by I noticed my forehead was getting puffier. Alarmed at the sudden onset, the petrified gal reported to the doctor, who informed her that she'd suffered an allergic reaction to an ingredient in the dye called PPD, Kennedy reported."

Woman, 26, reveals how allergic reaction to salon hair dye left her with chemical burns on her scalp and a severely swollen head. Nov. 8, 2021

https://www.dailymail.co.uk/femail/article-10177103/Woman-26-reveals-allergic-reaction-hair-dye-left-chemical-burns-swollen-head.html

A horrified woman revealed how she suffered allergic reaction to hair dye so severe she was left with an extremely swollen head and face and painful chemical burns.

Teenager reveals she 'felt like a monster' after allergic reaction to hair dye made her face swell so badly she couldn't see out of one eye Dec, 28, 2022

https://www.dailymail.co.uk/femail/article-11579181/Teenager-felt-like-monster-allergic-reaction-hair-dye.html

"Two days after dyeing my hair, I woke up with a liquid coming out of the scalp and the next day with my face swollen to the point where I couldn't open one of my eyes."

TO DYE FOR My face ballooned to twice its size after a reaction to salon hair dye & it's left me allergic to sunlight. Dec. 30, 2019

"AN OFFICE worker has revealed an allergic reaction to hair dye caused her face to balloon and almost killed her when her airways closed."

Reaction to hair dye leaves woman with scalp full of blisters and eyes swollen shut. Apr 2, 2021

https://metro.co.uk/2021/04/02/hair-dye-reaction-leaves-woman-with-blistered-scalp-and-swollen-eyes-14348259/

"Mum-of-four Leonie Dee was hospitalised after attempting to dye her hair at home using two different colours – Schwarzkopf Live in Cosmic Blue and Ultra Violet.

HAIR HORROR I was left blind for days and my face swelled up like a bowling ball after horror reaction to L'Oreal hair dye. Oct. 19, 2023

https://www.thesun.co.uk/fabulous/24415972/blind-face-swelled-horror-reaction-loreal-hair-dye/

"Saffron Veal, from Southampton, was left hospitalised after suffering a severe allergic reaction to a semi-permanent box dye last month."

Woman reveals she was left unable to open her EYES after an allergic reaction to drugstore hair dye caused her face to swell - and says it took four weeks to improve. Sept. 9 2020

https://www.dailymail.co.uk/femail/article-8713261/Woman-41-reveals-hair-dye-caused-face-balloon.html

"Hair stylist, Sherrie Virtue, 41, from Montreal, Quebec told how hair dye caused her face to balloon so much that she couldn't open her eyes and had to shave her head - and it took four weeks to improve."

THAT'S CRAZY' Mum was 'hospitalised three times after Nice 'n Easy hair dye reaction caused face to swell so badly she was unrecognizable. Feb 14, 2018

https://www.thesun.co.uk/news/5577391/nice-easy-hair-dye-reaction-allergy-face-swell/

Man's head ballooned like Megamind after severe hair dye reaction August 6 2024

https://metro.co.uk/2024/08/06/mans-head-ballooned-like-megamind-severe-hair-dye-reaction-21369522/

Man's eyes, neck swell in bizarre reaction to hair dye. Dec. 15, 2018

https://www.foxnews.com/health/mans-eyes-neck-swell-in-bizarre-reaction-to-hair-dye

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 3.3X toxicokinetic factor and a 3.3X 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.