ADMIN

Memo
Agenda
Minutes
MoS vs MoE

EXPERT PANEL MEETING
June 3-4, 2024

Cosmetic Ingredient Review

Commitment & Credibility since 1976

MEMORANDUM

To: The Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 169th Meeting of the Expert Panel — Monday and Tuesday, June 3rd – 4th, 2024
Date: May 10, 2024

Welcome to the second Panel Meeting of 2024! The agenda and accompanying materials for the 169th Expert Panel Meeting, to be held on June 3rd – 4th, 2024, are now available. ***The location is different from our meeting in March*** – and is in-person, at the Westin Georgetown, 2350 M St., NW, Washington, DC 20037. ***The meeting will start on both days at 8:30 AM EST***. The meeting is open to the public; no prior registration is required. While participation in this meeting will be exclusively in-person, audience members may view the meeting live, via MS Teams (note: there will be no option to participate in the discussions virtually). Invitations (3) to join the virtual component of the meeting may be received by request in advance of the meeting at the meeting page:

https://www.cir-safety.org/meeting/169th-expert-panel-meeting

The meeting agenda includes the consideration of 8 reports advancing in the review process, including 3 draft final reports, 1 draft tentative report, and 4 draft reports – 1 of which is a re-opened review and 1 or which is a revised draft report. Also on the agenda are 5 reports proposed for rereview. ***For the proposed rereviews, the Panel is only being asked if the reports should be reopened.*** There is also 1 administrative item with regard to margins of exposure vs safety. Additionally, dossiers relating to the potential use of read-across will be forwarded to the Read-Across Working-Group, with regard to the 2 reports, Prostaglandin Analogues and Fatty Amphocarboxylates, for review prior to this meeting.

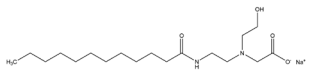
As we continue with our efforts to reduce the quantity of late breaking information, we are making a cutoff for nearly all information sent to the Panel. The exception to this cutoff is any pertinent information relevant to a Draft Final Report. (For this meeting, the only reports that fall into this category are PPD, THB, and Yeast.) ***Submissions received on non-final reports, after the issuance of the Wave 2 supplement on May 24th, will be held back until the next Panel review of those reports.***

Finally, we will have 2 presentations at this meeting. The first will be from Dr. David Allen, Senior Director, Human Health Sciences and Operations at the International Collaboration on Cosmetics Safety (ICCS), with regard to non-animal methodologies for ocular toxicity.

Our second presentation will be from Tom Myers, new President & CEO of the Personal Care Products Council (PCPC), to acknowledge the importance of the work of this Panel for the cosmetic industry, and to lend his support.

Draft Reports - There are 4 draft reports for review. Sufficient data to proceed, or issue an Insufficient Data Announcement (IDA)?

1. Fatty Amphocarboxylates – RevDR (Priya) – ***Dr. Cohen reports on day 2*** – This report was first reviewed at the June 2023 meeting, at which time the Expert Panel for Cosmetic Ingredient Safety (Panel) tabled the review for the reasons described herein. Prior to the June 2023 meeting, Wave 2 data were received containing information regarding several fatty acid chain mixtures (amphoacetates C8-18, amphoacetates C12-14, and amphoacetates C12) as well as REACH dossiers for 2 potential read-across ingredients (reaction products of 1H-imidazole-1-ethanol, 4-5-dihydro-, 2-(C11-17 and C17 unsatd. alkyl) derivs. and sodium hydroxide and 2-propenoic acid and *N*-(2-hydroxyethl)-*N*-[2-[(1-oxooctyl)amino]ethyl]-β-alanine). Accordingly, CIR staff has prepared read-across justification tables for representative mono- and diacetate forms of alkylamphoacetates as well as *N*-(2-hydroxyethl)-*N*-[2-[(1-oxooctyl)amino]ethyl]-β-alanine for analysis by the Read-Across Working Group (who will provide their analysis in the Panel team meetings).



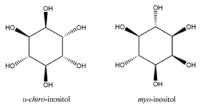
   The June 2023 Wave 2 submission also included information on ingredients being reviewed in this report. These data, along with new data found on Sodium Cocoamphopropionate, have been incorporated into the document. At the June 2023 meeting, the Panel decided to table the report for reorganization, noting that the following data (none of which has been received) are needed:

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

   It should be noted that of the 11 ingredients reviewed in this Revised Draft Report, 4 (i.e., Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate) have previously been reviewed by the Panel in a report published in 1990; the Panel concluded that these 4 ingredients are safe as used, as described in that report. Furthermore, these ingredients were rereviewed in 2008, at which time the Panel reaffirmed the original conclusion.

   Upon review, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or mixed conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

2. Inositol – DR (Priya) – ***Dr. Belsito reports on day 2*** – This is the first time the Panel is reviewing a safety assessment on this ingredient. A Scientific Literature Review (SLR) was announced on March 28, 2024.



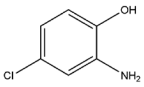
   Comments on the SLR that were received from the Council have been addressed and are included for your review. A submission from Council was received suggesting the inclusion of two reports found in the literature. These reports have been referenced in the Draft Report.

   It should be noted that there are 9 potential geometric isomers of Inositol. According to the *Dictionary*, the two isomers used in the production of cosmetic ingredients are myo-inositol and D-chiro-inositol. Data on both of these configurations have been included in the report (and the isomeric form is called out); however, not all studies stated the specific isomer of inositol used, and in these cases, "isomer unspecified" is noted in the study summary. The data profile included herein therefore indicates the availability of data for myo-inositol, D-chiro-inositol, and inositol (isomer unspecified).

   According to 2023 VCRP survey data, Inositol is used in 212 total formulations (185 leave-on formulations and 27 rinse-off formulations). The results of the concentration of use survey conducted by the Council in 2022 indicate Inositol is used at up to 2% (in face and neck products and in moisturizing products). Ocular exposure to Inositol may occur as this ingredient is used in products used near the eye (e.g., Inositol is used in eye lotion at up to 1%). In addition, mucous membranes are exposed and incidental ingestion may occur as Inositol is reported to be used in a lipstick formulation (concentration of use not provided). Inositol is used in a face powder formulation (concentration of use not provided), and could be incidentally inhaled

Upon review, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or mixed conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

3. 4-Chloro-2-Aminophenol – DAR (Christina) – ***Dr. Cohen reports on day 2*** – The Panel previously reviewed the safety of 4-Chloro-2-Aminophenol (and 5 other amino cresol hair dye ingredients) in an assessment that was published in 2004. In June 2022, the Panel re-opened the safety assessment for these ingredients due to some of these hair dyes, including 4-Chloro-2-Aminophenol, being banned for use in cosmetics by the European Commission. Because the Panel determined that data for these amino cresol hair dye ingredients could not be read-across, rather than including all 6 ingredients in one amended report, rereviews of each hair dye included in that original 2004 report have been presented as individual stand-alone reports; this is the last ingredient of the group to be brought to the Panel. In the original report, the Panel concluded that 4-Chloro-2-Aminophenol is safe for use in oxidative hair dyes, but the data were insufficient to support the safety of this ingredient in nonoxidative (semi-permanent) hair dyes.



According to 2023 VCRP survey data, 4-Chloro-2-Aminophenol has no reported uses. The results of the concentration of use survey conducted by the Council in 2021 also reported no uses. When the original safety assessment was published in 2004, 4-Chloro-2-Aminophenol was reported to have no uses, according to 1998 VCRP data and 1999 industry survey data.

Since the June 2022 meeting, no new data have been submitted for this ingredient. Upon review of this Draft Amended Report, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Amended Report with a safe as used, safe with qualifications, unsafe, or mixed conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

4. *Paeonia suffruticosa* – DR (Preethi) – ***Dr. Belsito reports on day 2*** – This is the first time the Panel has seen a safety assessment of these 5 cosmetic ingredients. An SLR was announced by CIR on March 19, 2024.

According to 2023 VCRP survey data, Paeonia Suffruticosa Root Extract is reported to be used in 213 formulations, 173 of which are leave-on formulations. The other ingredients in this report have 18 or fewer reported uses. The results of the concentration of use survey conducted by the Council in 2022 (and updated in 2024) indicate Paeonia Suffruticosa Root Extract also has the highest maximum reported concentration of use at up to 0.5% in paste masks and mud packs. Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, and Paeonia Suffruticosa Root Extract are reported to be used in products applied near the eye (concentrations of use not reported). Additionally, most of the ingredients are used in formulations that could come in contact with mucous membranes (e.g., Paeonia Suffruticosa Seed Oil at up to 0.0025% in bath soaps and detergents). Moreover, some of these ingredients are used in cosmetic powders and possibly cosmetic sprays, and may be incidentally inhaled; for example, Paeonia Suffruticosa Root Extract is reported to be used at 0.05% in face powders.

One ingredient reviewed in this report, Paeonia Suffruticosa (Tree Peony) Root Bark Extract, is not listed in the *Dictionary*; however, it had uses reported in the VCRP database in 2023, and is thus part of this review. Additionally, the root bark ingredient is commonly used in traditional Chinese medicine; however, there is ambiguity with regards to the specificity of genus and species and plant part used, as well as the extraction methodology for this ingredient. Accordingly, data on the root bark ingredient have been included, and the test substance is identified in the report as described in the literature.

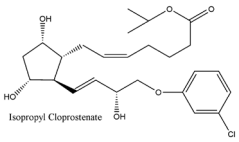
In response to the posting of the SLR, the comments and the following data were received and have been incorporated into this Draft Report:

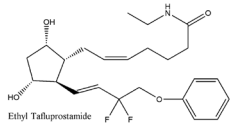
- Updated Concentration of Use by FDA Product Category: Paeonia suffruticosa-Derived Ingredients
- Repeated insult patch test (face mask containing 0.5% Paeonia Suffruticosa Root Extract).
- Summary Information - Paeonia Suffruticosa Root Extract (method of manufacture, impurities, and a 24-h closed patch test with 20 subjects)

Upon review, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or mixed conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

Draft Tentative Report - There is 1 draft tentative report for consideration. Issue a tentative conclusion or table with a deadline for return?

1. Prostaglandin Analogues – TR (Priya) – ***Dr. Belsito reports on day 2*** – This is the third time the Panel is seeing a safety assessment of these 2 cosmetic ingredients (and the second time as a Draft Tentative Report). At the December 2023 meeting, the Panel issued a second IDA for these ingredients, and requested the following data:





   - for Ethyl Tafluprostamide:
     - acute toxicity data
     - repeated dose toxicity data
     - developmental and reproductive toxicity data
     - in vivo genotoxicity data
     - information on targets and mechanisms
   - for Isopropyl Cloprostenate:
     - dermal irritation and sensitization data at the current maximum use concentration of 0.0075%
     - data on local ocular effects (intraocular pressure, iris color change) at current maximum concentration of use, with independent ophthalmologist to assess colorimetric data regarding iris color change
     - developmental and reproductive toxicity data
     - genotoxicity data
     - information on targets and mechanisms

Also at the December 2023 meeting, data were provided on potential read-across ingredients including tafluprost, travoprost, and cloprostenol. The use of cloprostenol as a read-across ingredient was previously rejected by the Panel; however, the Panel requested confirmatory data (e.g., receptor interaction studies and downstream profiles of adverse events) to determine if the use of tafluprost and travoprost are appropriate for use in this report. Prior to this meeting, the Read-Across Working-Group will be forwarded a dossier for review purposes (an analysis of which they may provide during Panel team meetings). Since the issuing of the second IDA, the following submissions have been received.

- Roadmap to Safety Assessment for Isopropyl Cloprostenate.
  - summary of information on Isopropyl Cloprostenate at 0.0075% that will be submitted in the future; this information includes:
    - QSAR assessment
    - HET-CAM assay
    - EpiOcular assay
    - HRIPT
    - 8-wk clinical assay
- Additional Data Supporting the Safe Use of Isopropyl Cloprostenate (up to 0.005%) in Cosmetics
  - summary of testing submitted previously using Isopropyl Cloprostenate at up to 0.005%
  - new data (which have been incorporated into the report):
    - Ames assay
    - In vitro micronucleus assay
  - summary of testing to be submitted in the future:
    - dermal metabolism and penetration assay
    - updated toxicological safety assessment with further substantiated read-across methodology
  - table presenting IDA requests along with request status/substantiation
- Roadmap for Ethyl Tafluprostamide/DDDE and request for extension to respond to the IDA
  - summary of information on Ethyl Tafluprostamide that will be submitted in the future; this information includes:

- receptor binding potency studies
- in vitro neutral red uptake assay
- ReproTracker assay
- Toxprofiler assay
- in silico endocrine receptor/activation predictions
- literature research of endocrine receptor activation by analogues
- analysis of differences in metabolism due to germinal fluorines in the suitability of analogues in read-across analyses
- report on read-across analyses

At the previous meeting, several presentations were made on this ingredient group. Links to these presentations are provided below:

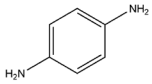
- Safety assessment of Ethyl Tafluprostamide as used in in cosmetic products - Petry & Mishra > Download PDF
- New Studies Support Safety of Isopropyl Cloprostenate in Cosmetics - Abramowitz & Weiss > Download PDF

Also at the December 2023 meeting, the Panel reviewed the Margin of Safety (MoS) calculations that were performed using systemic points of departure (PoD) derived from chemicals similar to Ethyl Tafluprostamide and Isopropyl Cloprostenate (i.e., an NOAEL at 0.0003 mg/kg bw/d for tafluprost and an LOAEL at 0.00012 mg/kg bw/d for travoprost, respectively). The Panel requested an adjustment factor of 3 be applied for the extrapolation from LOAEL to NOAEL for travoprost. Consequently, the MoS for Isopropyl Cloprostenate was recalculated using the derived NOAEL of 0.00004 mg/kg bw/d for travoprost.

The Panel should carefully consider and discuss the data (or lack thereof), and the draft Abstract and draft Discussion presented in this report. A Tentative Report with a safe as used, safe with qualifications, insufficient, split, or unsafe conclusion should then be issued. Alternatively, after review of the received documents, the Panel may wish to table this report. If this is the case, the Panel should set a firm deadline for when this report will be returned for their review.

Draft Final Reports - There are 3 Draft Final Reports for consideration. - Review these drafts, especially the rationale provided in the Discussion sections, and issue final reports, as appropriate.

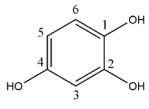
1. *p*-Phenylenediamine – FAR (Christina) – ***Dr. Cohen reports on day 2*** – At the December 2023 meeting, the Panel issued a Tentative Amended Report with the conclusion that *p*-Phenylenediamine, *p*-Phenylenediamine HCl, and *p*-Phenylenediamine Sulfate are safe for use as hair dye ingredients in the present practice of use and concentration described in the safety assessment.



   Since the December meeting, no unpublished data have been received for this report. Comments provided by the Council on the Tentative Amended Report have been addressed. Comments from WVE were also received and included with the report materials.

   The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Amended Report.

2. 1,2,4-Trihydroxybenzene – FR (Christina) – ***Dr. Belsito reports on day 2*** – At the December 2023 meeting, the Panel concluded that 1,2,4-Trihydroxybenzene is safe for use as a hair dye ingredient in the present practices of use and concentration described in this safety assessment.



   No additional data have been received for this report. Comments provided by the Council on the Tentative Report have been addressed.

   The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

3. Yeast – FR (Priya) – ***Dr. Cohen reports on day 2*** - At the December 2023 meeting, the Panel issued a Tentative Report on these 56 yeast-derived ingredients with the conclusion that 11 yeast-derived ingredients and 22 generically-named yeast-derived ingredients,

when derived from species of yeast included in the report with both dermal sensitization and food use status, are safe in cosmetics. The Panel determined that the data were insufficient to make a determination for the remaining 23 ingredients. Since the issuing of the Tentative Report, the following information has been received:

- Summary information *Candida oleophila* (includes a summary of an HRIPT).
    - EFSA statement – *Candida oleophila* has been added as a synonym to *Yarrowia lipolytica*; therefore, the QPS status that is currently present for *Yarrowia lipolytica*, is extended to *Candida oleophila*
    - Summary of an HRIPT on a Yeast Extract derived from *Candida oleophila* (final test concentration of 0.285%; n = 100)

- Composition and Use Information Pichia Heedii Extract and Yeast Extract made from *Pichia naganishii;* Summary of Food Use of *Pichia* spp.
    - composition information on Pichia Heedii Extract
    - composition information on a Yeast Extract derived from *Pichia naganishii*
    - reported use concentration of Pichia Heedii Extract in skin care products at up to 0.096%
    - reported use concentration of Yeast Extract derived from *Pichia naganishii* in skin care products at up to 0.105%
    - summary information/bibliography of *Pichia* spp. used in foods (it should be noted that the majority of the species (excluding *Pichia naganishii)* provided in the summary and noted in the references in the bibliography are not species that are reported to be used in cosmetics)

- Confirmation of skin compatibility and absence of allergenic potential of one cosmetic product after repeated application under patch.
    - HRIPT of a trade name mixture containing 10% Pichia Ferment Lysate Filtrate (n = 55; further test article details not provided)

- *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay
    - Ames assay on pure Pichia Ferment Lysate Filtrate

- In vitro eye irritation: human cornea model test – OECD 492
    - In vitro ocular irritation assay on pure Pichia Ferment Lysate Filtrate

- Information on Lipomyces Oil Extract and Lipomyces Lipid Bodies
    - manufacturing information on Lipomyces Oil Extract
      composition data on Lipomyces Lipid Bodies and Lipomyces Oil Extract
    - information regarding the potential use of Lipomyces Lipid Bodies as a loading agent for hydrophobic drugs and active ingredients

In addition to the information above, it should be noted that according to the *Dictionary*, Yeast Ferment Extract is derived from *Saccharomyces cerevisiae*; therefore, this ingredient may be considered safe as a non-generic yeast-derived ingredient. According to all of the information received, and the current method the Panel has employed to determine the safety of the ingredients in this report, the following ingredients may be considered for addition to the list of safe ingredients as they now have both QPS or GRAS status/food use/systemic toxicity data and sensitization data:

<u>Yeast-derived ingredients:</u>
Yarrowia Lipolytica Extract
Yarrowia Lipolytica Ferment Lysate
Yarrowia Lipolytica Oil
Yeast Ferment Extract

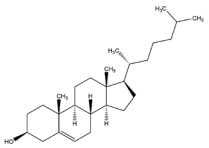
<u>Generic yeast-derived ingredients:</u>
Yeast Extract derived from *Candida oleophila*
Yeast Extract derived from *Pichia naganishii*

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report.

If these are satisfactory, the Panel should issue a Final Report.

Abbreviated Rereview (i.e., rereview proposal) – There are 6 rereview documents. Because it has at least been 15 years since the previous review was published, in accordance with CIR Procedures, the Panel is only being asked if the report should be reopened.

1. Cholesterol – RR (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Cholesterol in 1986. On the basis of the available information presented in the report, the Panel concluded that Cholesterol is safe as used in the present practices of use (as described in the safety assessment). The Panel previously considered a rereview of this report and reaffirmed the 1986 conclusion, as published in 2006.

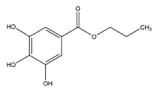


An extensive search of the world's literature was performed as of April 2024 for studies dated 2001 forward. A plant-based method of manufacture, and a few studies on acute toxicity, dermal irritation and sensitization, and ocular irritation were found. An historical overview, comparison of original and new use data, and the search strategy used are included herein.

According to 2023 FDA VCRP data, Cholesterol has 494 reported uses; in 2002, 258 uses were reported. In 2022, the maximum reported concentration of use for Cholesterol was at up to 0.25% in non-spray face and neck preparations (as well as non-spray and non-powder moisturizing products), compared to at up to 3% in eye lotions and foundations, as reported in 2002. Reported uses have nearly doubled and concentrations of use have decreased. There are 5 newly reported uses in baby products.

If upon review of the updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting.

2. Propyl Gallate – RR (Preethi) – ***Dr. Belsito reports on day 2*** - The Panel first published a review of the safety of Propyl Gallate in 1985. On the basis of the available information presented in the report, the Panel concluded that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1%. The Panel decided to reopen this report during the first rereview, to consider the sensitization potential of Propyl Gallate (as seen in patch testing results) and to possibly revise the recommended clinical margin of safety. Based on the data evaluated during the rereview process, the Panel concluded that Propyl Gallate is safe in cosmetic products at concentrations up to 0.1%, as published in 2007.

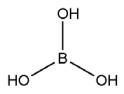


An extensive search of the world's literature was performed as of April 2024 for studies dated 2002 forward. A few updated regulatory limits for human and animal consumption, in vitro genotoxicity, in vitro developmental and reproductive toxicity studies, studies on estrogenic and anti-carcinogenic effects, and numerous clinical patch test case reports were found.

According to 2023 FDA VCRP data, Propyl Gallate has 86 reported uses; in 2002, 164 uses were reported. In 2023, the maximum reported concentration of use for Propyl Gallate was at up to 0.012% in eyeliners, compared to at up to 0.1% in other personal cleanliness products, as reported in 2003. Reported uses and concentrations of use have decreased significantly. No new use categories are reported to be in use.

If upon review of the updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting.

3. Boric Acid – RR (Preethi) – ***Dr. Cohen reports on day 2*** - The Panel first published a review of the safety of Boric Acid and Sodium Borate in 1983. On the basis of the available information presented in the report, the Panel concluded that Boric Acid and Sodium Borate are safe as used at $\leq$ 5% in the present practices of use (as described in the safety assessment) and that cosmetics containing free Sodium Borate or Boric Acid should not be used on infant or injured skin. The Panel previously considered a rereview of this report and reaffirmed the 1983 conclusion, as published in 2006.

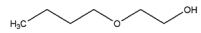


An extensive search of the world's literature was performed as of April 2024 for studies dated 2001 forward. A number of studies evaluating repeated dose oral and inhalation toxicity, reproductive and developmental effects of Boric Acid, and in vitro genotoxicity studies, have been found. An ocular irritation study evaluating Sodium Borate, a few studies on topics of interest (e.g., evaluating the potential hormonal, immunologic, and neurotoxic effects of Boric Acid), a few case reports, and several occupational exposure studies were also

found.

According to 2023 FDA VCRP data, Sodium Borate has 30 reported uses and Boric Acid has 8 reported uses; at the time that these ingredients were last considered for rereview, 265 and 77 uses were reported, respectively. In 2022, the maximum reported concentration of use for Sodium Borate is at 0.78% in other shaving preparations, compared to at up to 3% in skin fresheners as reported in 2002. Boric Acid has no reported concentrations of use in 2022. Overall, reported use categories have not changed significantly; however, reported uses and concentrations of use have significantly decreased for both ingredients.

If upon review of the updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting.

4. Butoxyethanol – RR (Christina) – ***Dr. Belsito reports on day 2*** -  The original review of Butoxyethanol was published in 1996 with the conclusion that "Butoxyethanol is safe in hair and nail products at concentrations up to 10.0%." In 2002, the Panel considered a rereview of this report for the first time and reaffirmed the original conclusion, as published in 2005.

   In April 2024, an extensive search of the world's literature was performed for studies dated 2000 forward. Many new studies have been identified in the published literature. It should be noted that at the time the original report was written, no restrictions for Butoxyethanol for use in cosmetic products were in effect in Europe; however, European regulations regarding cosmetic ingredients now categorize Butoxyethanol in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down. Butoxyethanol may only be used as a solvent in oxidative hair dye products at up to 4.0% and as a solvent in non-oxidative hair dye products at up to 2.0%, and must not be used in aerosol dispensers (sprays).

   In 2001, Butoxyethanol was reported to be used in 110 cosmetic formulations, with the majority of uses reported in hair dyes and colors. However, no concentrations of use were reported for hair dye formulations in response to the Council's 2001 survey; the maximum concentration of use range was reported to be 3 - 50%, with the highest concentration of 50% reported in nail polish and enamel removers. According to 2023 FDA VCRP data, Butoxyethanol was reported to be used in 3 hair dye formulations. No concentrations of use were reported in the Council's 2020 survey.

   If upon review of the new studies and updated use data the Panel determines that the Butoxyethanol safety assessment should be re-opened for review, a Draft Amended Report will be presented at an upcoming meeting.

5. Potassium Cocoyl Hydrolyzed Collagen – RR (Thushara) – ***Dr. Cohen reports on day 2*** - The Panel first published a review of the safety of Potassium-Coco-Hydrolyzed Animal Protein and Triethanolamine-Coco-Hydrolyzed Animal Protein in 1983. The Panel concluded that Potassium-Coco-Hydrolyzed Animal Protein and Triethanolamine-Coco-Hydrolyzed Animal Protein are safe as cosmetic ingredients in the present practices of use as described in that report. Please note that the names of these two ingredients have been subsequently changed, and are they are now listed in the *Dictionary* as Potassium Cocoyl Hydrolyzed Collagen and TEA-Cocoyl Hydrolyzed Collagen, respectively. The Panel previously considered a rereview of these two ingredients in 2002 and reaffirmed the 1983 conclusion, as published in 2005

   In April 2024, an extensive search of the world's literature was performed for studies dated year 2000 forward. All these searches employing many different search strategies clearly indicated that there were no significant scientific developments or changes in safety information that had been reported.

   In 2001, Potassium Cocoyl Hydrolyzed Collagen was reported to be used in 64 cosmetic formulations, with the majority of uses reported in hair preparations. The Council's 2001 survey reported a maximum concentration of use range of 0.05 - 20%, with the highest concentration of 20% reported in shampoos (non-coloring). According to 2023 FDA VCRP data, there was 1 use in an eye lotion and 1 in a shamposs (non-coloring) for Potassium Cocoyl Hydrolyzed Collagen; no concentrations of use were reported in the Council's 2022 survey. Also in 2001, TEA-Cocoyl Hydrolyzed Collagen was reported to be used in 20 cosmetic formulations, with the highest frequency of use (4 uses) reported in cleansing products. The Council's 2001 survey reported a maximum concentration of use of1% in bubble baths. According to 2023 FDA VCRP data, there were no reported uses for TEA-Cocoyl Hydrolyzed Collagen; no concentrations of use were reported in the Council's 2022 survey.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a full Draft Amended Report will be presented at an upcoming meeting.

Administrative Item - there is 1 administrative item.

1. MoS v MoE – Admin (Jinqiu) – ***Dr. Belsito reports on day 2*** – The Panel is requested to review the comments and determine whether it is appropriate to make such changes in reports and to distinguish between MoS and MoE in this manner.

Full Panel Meeting

The Panel will consider the 3 reports to potentially be issued as Final Reports, followed by the remaining reports advancing in the process (i.e., the Tentative Report and Draft Reports). In addition, a consensus should be reached for each of the 5 rereview documents, and the use of MoE vs MoS.

Please remember, the meeting starts at 8:30 AM EST on day 1 and day 2.

Looking forward to seeing you all ***in-person***!

Agenda
169th Meeting of the Expert Panel for Cosmetic Ingredient Safety
June 3rd – 4th, 2024

Monday, June 3, 2024

8:30 AM	**WELCOME TO THE 169th EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:45 AM	**PRESENTATION – NAMs - ocular irritation**	**Dr. David Allen (ICCS)**
9:45 AM	**REMARKS – new PCPC President & CEO**	**Tom Myers, J.D. (PCPC)**
10:15 AM - 5 PM	**TEAM MEETINGS**	**Drs. Belsito/Cohen**

Dr. Cohen's Team*

Admin (JZ)	MoS vs MoE
TR (PC)	Prostaglandin analogues
FR (PC)	Yeast
RevDR (PC)	Fatty Amphocarboxylates
DR (PC)	Inositol
RR (TD)	Potassium Cocoyl Hydrolyzed Collagen
FR (CB)	1,2,4-Trihydroxybenzene
FAR (CB)	*p*-Phenylenediamine
DAR (CB)	4-Chloro-2-Aminophenol
RR (CB)	Butoxyethanol
DR (PR)	*Paeonia suffruticosa*
RR (PR)	Cholesterol
RR (PR)	Boric Acid
RR (PR)	Propyl Gallate

Dr. Belsito's Team

RR (CB)	Butoxyethanol
FAR (CB)	*p*-Phenylenediamine
DAR (CB)	4-Chloro-2-Aminophenol
FR (CB)	1,2,4-Trihydroxybenzene
Admin (JZ)	MoS vs MoE
DR (PR)	*Paeonia suffruticosa*
RR (PR)	Cholesterol
RR (PR)	Boric Acid
RR (PR)	Propyl Gallate
FR (PC)	Yeast
TR (PC)	Prostaglandin analogues
RevDR (PC)	Fatty Amphocarboxylates
DR (PC)	Inositol
RR (TD)	Potassium Cocoyl Hydrolyzed Collagen

The purpose of the Cosmetic Ingredient Review and the Expert Panel for Cosmetic Ingredient Safety is to determine those cosmetic ingredients for which there is a reasonable certainty, in the judgment of competent scientists, that the ingredients are safe under intended conditions of use.

FR: Final Report || FAR: Final Amended Report || TR: Tentative Report || TAR: Tentative Amended Report || DR: Draft Report || DAR: Draft Amended Report || RR: Re-Review || RRsum: Re-Review Summary || Rev: Revised || SM: Strategy Memo || Admin: Administrative item

BH: Bart Heldreth || MF: Monice Fiume || CB: Christina Burnett || PC: Priya Cherian || TD: Thushara Diyabalanage || PR: Preethi Raj || JZ: Jinqiu Zhu

*Team moves to the breakout room.

Tuesday, June 4, 2024			
8:30 AM	**WELCOME TO THE 169th FULL EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:40 AM	Admin **MINUTES OF THE MARCH 2024 EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:45 AM	**DIRECTOR'S REPORT**		**Dr. Heldreth**
9:00 AM	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**		
	Final Reports		
	FAR (CB)	*p*-Phenylenediamine – ***Dr. Cohen reports***	
	FR (CB)	1,2,4-Trihydroxybenzene – ***Dr. Belsito reports***	
	FR (PC)	Yeast ingredients – ***Dr. Cohen reports***	
	Reports Advancing		
	TR (PC)	Prostaglandin Analogues – ***Dr. Belsito reports***	
	RevDR (PC)	Fatty Amphocarboxylates – ***Dr. Cohen reports***	
	DR (PC)	Inositol – ***Dr. Belsito reports***	
	DAR (CB)	4-Chloro-2-Aminophenol – ***Dr. Cohen reports***	
	DR (PR)	*Paeonia suffruticosa*-derived ingredients – ***Dr. Belsito reports***	
	Other Items		
	RR (PR)	Cholesterol – ***Dr. Cohen reports***	
	RR (PR)	Propyl Gallate – ***Dr. Belsito reports***	
	RR (PR)	Boric Acid – ***Dr. Cohen reports***	
	RR (CB)	Butoxyethanol – ***Dr. Belsito reports***	
	RR (TD)	Potassium Cocoyl Hydrolyzed Collagen – ***Dr. Cohen reports***	
	Admin (JZ)	MoS vs MoE – ***Dr. Belsito reports***	

ADJOURN – *The next will be held in-person on **September 30 – October 1, 2024** at the Westin Georgetown Hotel, 2350 M Street, N.W., Washington, DC. Please check the CIR website for details as the meeting approaches*

On the basis of all data and information submitted, and after following all of the Procedures (https://www.cir-safety.org/supplementaldoc/cir-procedures), the Expert Panel shall determine whether each ingredient, under each relevant condition of use, is safe, safe with qualifications, unsafe, or there are insufficient data or information to make a determination of safety. Upon making such a determination, the Expert Panel shall issue a conclusion and/or announcement.

FR: Final Report || FAR: Final Amended Report || TR: Tentative Report || TAR: Tentative Amended Report || DR: Draft Report || DAR: Draft Amended Report || RR: Re-Review || RRsum: Re-Review Summary || Rev: Revised || SM: Strategy Memo || Admin: Administrative item

BH: Bart Heldreth || MF: Monice Fiume || CB: Christina Burnett || PC: Priya Cherian || TD: Thushara Diyabalanage || PR: Preethi Raj || JZ: Jinqiu Zhu

ONE HUNDRED SIXTY-EIGHTH MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

March 28-29, 2024

Microsoft Teams Virtual Meeting

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairperson

Donald V. Belsito, M.D., Teamleader

David E. Cohen, M.D., Teamleader

Curtis D. Klaassen, Ph.D.

Allan E. Rettie, Ph.D.

David Ross, Ph.D.

Thomas J. Slaga, Ph.D.

Paul W. Snyder, D.V.M., Ph.D.

Susan Tilton, Ph.D.

Liaison Representatives

Consumer

Courtney Griffin, J.D.

Industry

Alex Kowcz, M.B.A.

Government

Hong Xie, Ph.D.

Jannavi Srinivasan, Ph.D.

Prashiela Manga, Ph.D.

Janet Zang, Ph.D.

_____

Adopted (Date)

_____

Wilma F. Bergfeld, M.D.

CIR Staff

Administration
Bart Heldreth, PhD - Executive Director

Monice Fiume, MBA - Senior Director

Carla Jackson - Administrative Coordinator

Subject Matter Expertise
Jinqiu Zhu, PhD, DABT, ERT, DCST - Toxicologist

Analysis
Christina L. Burnett, MSES - Senior Scientific Analyst

Priya Cherian, MS - Senior Scientific Analyst

Preethi S. Raj, MS - Senior Scientific Analyst

Thushara Diyabalanage, Ph.D.–Senior Scientific Analyst

Information Services
Kevin Stone Fries, MLS - Information Services Manager

Other Meeting Attendees

Name	*Organization*
Yunqi An	Victoria's Secret & Co.
John Bailey	JEB Consulting
Don Bjerke	Procter & Gamble
Connie Cheung	unidentified
AJ Cuevas	Combe
Silvia Pérez Damonte	CLAIM
Carol Eisenmann	Personal Care Products Council
Christine Maza Ferrerira	unidentified
Linda Giles	Transcription, Etc.
Kyu-Bong Kim	unidentified
Miao Li	unidentified
Kathleen McCann	Consumer Federation of America
Sanghamitra Mishra	unidentified
Jeffrey Nicolai	Performance Beauty Group
Kimberly Norman	Personal Care Products Council
Thomas Petry	ToxMinds BVBA
Matteo Zanotti Russo	Angel Consulting SAS
Prajakta Shimpi	L'Oreal USA
Brenda Shinyashiki	Edgewell Personal Care
Kathy Stanton	Personal Care Products Council
Jan Summers	unidentified
Laura Turnham	Swift Fox Consultancy
Patra Volarath	US FDA
Zemin Wang	US FDA
Miao Wang	L'Oreal
Teresa Washington	unidentified
Nicolas Wolf	unidentified
Merle Zimmermann	American Herbal Products Association

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 168th meeting of the Expert Panel for Cosmetic Ingredient Safety. Dr. Bergfeld noted that the Panel reviewed 8 ingredient reports, including 1 final, 1 tentative, 6 draft reports, 1 re-review, and 2 re-review summaries. Dr. Bergfeld also noted that the Panel spent time on a few administrative documents, including the exposure and risk strategy memo and accompanying comments from the CIR Science and Support Committee, a strategy memo on dibutyl phthalate and accompanying comments from Women's Voices for the Earth, and the 2024 Priorities. Dr. Bergfeld announced the Read-Across Working group held their first meeting and elected Dr. Allan Rettie as the Chairperson of that committee. The committee also includes Dr. Curt Klaassen, Dr. David Ross, Dr. Susan Tilton, Dr. Don Bjerke, and will invite former Panel member, Dr. Dan Liebler, as a consultant.

Dr. Bergfeld thanked the CIR staff, the CIR Science and Support Committee, the Council, and the Panel for their support and expressed appreciation for the comments from the Women's Voices for the Earth.

APPROVAL OF MINUTES

The minutes of the December 4-5, 2023 (167th) Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth thanked the members of and liaisons to the Panel. He noted that a new sub-group of the Panel, the CIR Read-Across Working-Group, held an initial meeting on the general topic of read-across. The Panel also reviewed administrative items regarding exposure, risk, priorities, and strategies for the review of Dibutyl Phthalate. With specific note on Dibutyl Phthalate and future ingredient re-reviews wherein use has been discontinued, he noted a proposal to the CIR Steering Committee to add a new conclusion category of "use not supported," citing lack of use and concentration data. At this meeting, the Panel also welcomed a new CIR Senior Scientific Analyst, Dr. Thushara Diyabalanage.

FINAL SAFETY ASSESSMENTS

None.

TENTATIVE SAFETY ASSESSMENTS

4-Amino-*m*-Cresol
The Panel issued a Tentative Amended Report for public comment with the conclusion that 4-Amino-*m*-Cresol is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment. The Panel previously reviewed this ingredient as part of a larger group of amino cresol hair dyes; however, because the Panel determined that data for these amino cresol hair dye ingredients could not be read-across the group, re-reviews of each hair dye included in that original 2004 report are now presented as individual stand-alone reports.

4-Amino-*m*-Cresol is reported to function as an oxidative hair dye in hair coloring products. The Panel recognizes that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel expects that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

The Panel noted that the available toxicokinetic studies show that 4-Amino-*m*-Cresol absorbs slowly through the skin, is not genotoxic, is not a developmental or reproductive toxicant, is not a dermal irritant, and has low concentrations of use. Additionally, a margin of safety (MOS) calculation yielded a result greater than 100, which is generally considered to be protective. However, the Panel further deliberated on incorporating the skin absorption data presented in the report for calculating the MOS, rather than relying on the conservative estimate of 50% absorption. The Panel considered these findings, coupled with the short exposure time as a rinse-off product, and determined that the data are sufficient to conclude that 4-Amino-*m*-Cresol is safe as a hair dye ingredient in the present practices of use and concentration.

Lanolin-Derived Ingredients
The Panel issued a Tentative Amended Report for public comment with the conclusion that the following 9 lanolin-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Acetylated Lanolin	Hydroxylated Lanolin	Lanolin Alcohol
Acetylated Lanolin Alcohol	Lanolin	Lanolin Oil
Hydrogenated Lanolin	Lanolin Acid	Lanolin Wax

The Panel discussed the "lanolin paradox" where Lanolin may cause allergic contact dermatitis when applied to damaged skin, but allergenicity does not appear in these apparently sensitized patients when Lanolin is applied to normal, healthy skin in patch tests. The rate of allergic reaction to Lanolin is extremely low in the general population, and sensitization can be further reduced when Lanolin is ultra refined to reduce the amount of free Lanolin Alcohol. The Panel cautioned that Lanolin should not be used on damaged skin, especially in high-risk populations for sensitivity (e.g., pediatric and geriatric populations).

Toluene
The Expert Panel issued a Tentative Amended Report for public comment with the conclusion that Toluene is safe at up to 20% in nail products. According to 2023 VCRP survey data, Toluene is not reported to be used; however, the 2023 concentration of use survey conducted by the Personal Care Products Council (Council) indicate that Toluene is used at up to 20% in nail polish and enamel. Other uses were reported in the survey at low concentrations; however, these concentrations refer to Toluene as an impurity in cosmetic products and are thus not relevant to the purposes of this report.

The safety of this ingredient in nail products was supported by a lack of irritation and sensitization in human assays and conservative MOS calculations yielding values above 100. However, the Panel requested additional MOS calculations be conducted by using a point of departure (POD) for the developmental and reproductive toxicity (DART) endpoint. The Panel noted the potential for Toluene to result in reproductive and endocrine toxicity; however, this concern was

mitigated as these effects were observed at high concentrations not relevant to cosmetic exposure. (It was also noted that occupational exposure is not within the purview of the Panel.) The Panel also noted regulations from the California Department of Toxic Substances Control (DTSC) mandating that manufacturers of nail products certify that their products do not contain more than 100 ppm Toluene. After review of the data for each endpoint, the Panel could not come to the conclusion that Toluene should not exceed 100 ppm in nail products, and instead determined that Toluene is safe in nail products at the current maximum use concentration of 20%.

MIBK
The Panel issued a Revised Tentative Amended Report for public comment concluding that MIBK is safe as used in nail polish removers and as an alcohol denaturant in cometic products. The Panel determined that the use of MIBK as an alcohol denaturant in cosmetic products should not be more than 4% MIBK in alcohol; it was emphasized that this usage should not be misconstrued as not more than 4% MIBK present in a final formulation. The Panel also noted that the reports of MIBK-induced renal changes observed in studies were due to a male rat specific mechanism of action and should not be considered a human health concern.

Pentapeptides
The Panel issued a Tentative Report for public comment with the conclusion that Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The amino acid sequence of the pentapeptide portion of these ingredients can vary; one sequence is lysine-threonine-threonine-lysine-serine (i.e., Lys-Thr-Thr-Lys-Ser, or KTTKS), and the other is Lys-Thr-Ser-Lys-Ser (or KTSKS). The Panel found the information in the report sufficient to apply the conclusion to both sequences.

The Panel noted that although human repeated insult patch tests (HRIPT) were not performed at maximum use concentrations, the negative results obtained in these studies, in conjunction with the negative results observed in chemico and in vitro, mitigated any concern regarding sensitization. Additionally, the negative human dermal irritation studies at less than the maximum use concentration were supported by a negative in vitro study. The Panel also considered the low reported maximum concentration of use for these ingredients, limited percutaneous absorption in the skin, negative genotoxicity data, absence of endocrine disruption at a concentration of 0.12%, and method of manufacturing and impurities data for Palmitoyl Pentapeptide-4. Furthermore, the Panel considered their previous safety review of the individual amino acids, as well as myristic acid and palmitic acid, comprising these ingredients which were determined to be safe as used in cosmetics.

BHA
The Panel issued a Tentative Amended Report for public comment with the conclusion that BHA is safe in cosmetics in the present practices of use and concentration described in the safety assessment. A safety assessment on BHA was first published in 2005, with a conclusion of safe as a cosmetic ingredient in the present practices of use (as described in the safety assessment); that conclusion was reaffirmed, as published in 2006. A re-review was initiated at the June 2023 Panel meeting to evaluate potential endocrine and reproductive effects of BHA at high doses and to provide an updated assessment of the safety of this ingredient.

The Panel concurred with the Discussion presented in the original (1984) report. In addition, the Panel considered the developmental and reproductive toxicity and endocrine studies presented in the updated report, and stated that any developmental and reproductive, endocrine, androgenic, and estrogenic effects that were observed were seen primarily in cell systems and at non-physiological concentrations, thus mitigating any concerns. The Panel also noted the generally recognized as safe (GRAS) for use in foods in the US, and stated that the exposure assessment included in the document was useful when evaluating safety.

***t*-Butyl Alcohol**
The Panel issued a Tentative Amended Report for public comment with the conclusion that *t*-Butyl Alcohol is safe in cosmetics in the present practices of use and concentration described in the safety assessment. The last safety assessment on this ingredient was published in 2005, with a conclusion of safe as used in cosmetic products. A re-review was initiated at the September 2023 Panel meeting to evaluate developmental and reproductive toxicity effects seen at 1% (which is comparable to the highest reported concentration of use), to update the previous discussion of carcinogenicity, and to rectify the erroneous test concentration stated in a previously reviewed HRIPT.

The Panel determined that a negative guinea pig maximization test mitigated a need for confirmatory sensitization data at maximum concentration of use. The Panel discussed the carcinogenicity studies and determined that the weight-of-evidence does not support a carcinogenic effect. Also, the Panel was in agreement with the Discussion in the 2005 report which stated that effects of *t*-Butyl Alcohol on development were likely secondary to maternal toxicity and effects on learning development were attributed to *t*-Butyl Alcohol in maternal milk and were not an in utero effect. Finally, the Panel noted that because undiluted *t*-Butyl Alcohol was an ocular irritant, ocular irritation data at maximum use concentration would add to the robustness of the safety assessment.

INSUFFICIENT DATA ANNOUNCEMENTS

Copper Gluconate
The Panel issued an insufficient data announcement (IDA) for Copper Gluconate. The additional data needed to determine the safety of this ingredient are:

- Impurities data for Copper Gluconate as used in cosmetics
- Dermal irritation and sensitization data at maximum concentration of use
- Ocular irritation data, if available

RE-REVIEWS

In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued safety assessments approximately every 15 years. At this meeting, the Panel considered the previous assessment of Pyrogallol for re-review. The Panel reopened this safety assessment to incorporate and discuss the findings of the National Toxicology Program 2-year carcinogenicity study that was published in 2013, as well as any additional relevant data that has been published since the report was last reviewed. The Panel noted that this hair dye ingredient has only one reported use in hair coloring products and no reported concentrations of use. The Panel advised that current use (frequency and concentration) data and dermal irritation test data at up to the previously reported maximum use concentration

of 5% are needed to aid the Panel in determining a potential revised conclusion. A Draft Amended Report will be presented to the Panel for this safety assessment at a future meeting.

RE-REVIEW SUMMARIES

Once the Panel determines to not reopen a previously-issued safety assessment, thereby reaffirming the existing conclusion, a re-review summary is prepared. The Panel approved the following 2 re-review summaries:

- Sodium Carbonate
- VA/Crotonates Copolymer

READ-ACROSS WORKING GROUP – "…30% CHEMISTRY, 70% CONTEXT…."

The Panel has been utilizing read-across strategies for a number of years. One early example can be found in the Alkyl PEG Ethers report, affording the safety assessment of 369 ingredients in one report, even though there were data gaps for numerous ingredients therein (if read-across was not used). With the trend away from new animal studies and toward new approach methodologies (NAMs), the necessity of utilizing read-across strategies is ever increasing. And the complexities of these strategies are often well beyond simple interpolations between various length straight-chain hydrocarbons or various numbers of ethoxy repeat units.

At this 1st meeting of the Read-Across Working-Group (RAWG), the Panel Chairperson, Dr. Wilma Bergfeld, appointed Panel member, Dr. Allan Rettie, as the chair of the RAWG. The RAWG comprises Dr. Rettie, as well as Drs. Tilton, Klaassen, and Ross. As a sub-group of the Panel, the RAWG does not make any final ingredient safety decisions or even vote (when acting as the sub-group). Instead, this sub-group is charged with determining what parameters are needed, on a case-by-case (report-by-report or ingredient-by-ingredient) basis, and to propose a threshold of confidence (or lack thereof) to the full Panel, wherein a read-across strategy is utilized. Essentially, the RAWG is charged in each case with determining if the provided data and associations between read-across source(s) and target(s) are sufficient and valid, and that there is a consensus of confidence (or lack thereof) in the strategy for filling a specific data gap. The members of the RAWG agreed to these notions and will proceed with supporting the full Panel with their analyses of such strategies, on a case-by-case basis.

EXPOSURE AND RISK

The Panel reviewed an exposure assessment strategy memo and endorsed the integration of exposure assessments into CIR reports whenever feasible. The Panel agreed that transparent estimates of exposures across different product categories are crucial for effectively assessing risk. The Panel further discussed the need and feasibility of estimating cumulative exposures from multiple product categories compared to identifying and clarifying a single category that poses the highest systemic exposure.

The Panel also reviewed the CIR Science and Support Committee's (SSC's) comments and reached a consensus that the inclusion of a quantitative systemic risk assessment should be determined on a case-by-case basis. The Panel acknowledged the significance of transparent exposure and systemic risk assessments; in cases where a margin of safety is deemed not applicable, the Panel asks for an explanation to be provided in the discussion to ensure transparency and clarity. Additionally, the Panel recognizes that the need for margins of safety can vary depending on endpoints of concern and should be established based on valid points of departure (e.g., NOAELs and LOAELs), which are identified and substantiated by the data included in the report.

DRAFT PRIORITIES

There are 18 reports docketed, covering 31 ingredients, on the 2024 Final Priorities List. Reports previously prioritized and on the CIR docket, as well as an extensive number of re-reviews of previous assessments, will supplement the total number of reports/ingredients to be assessed in 2024, and beyond. Additionally, with modernization efforts to better utilize in silico tools (e.g., DEREK), NAMs, Cosmetics Direct (the US FDA mandatory reporting program to replace the now defunct voluntary program, VCRP), formalized exposure and risk assessments (when warranted), and read-across (including proposals of the RAWG), CIR proposed that there is plenty of substance on the Panel's docket to extend through the end of 2025.

The Panel agreed with the proposal to make no frequency-of-use-based ingredient report additions to the Panel's docket in the coming year. However, if any interested party would like to request an ingredient review for cause (including: highlighting a potential risk/safety concern, accompanied with supporting data/information), CIR would be happy to present these to the Panel for potential prioritization. To make a request for cause, please provide a complete submission to CIR no later than May 3rd, 2024.

PHTHALATES STRATEGY

The Panel discussed the strategy of the preparation of the Draft Amended Report for Dibutyl Phthalate. The Panel reopened the report on this ingredient in 2023 after the FDA petitioned the Panel to accelerate its re-review. The Panel determined that Diethyl Phthalate and Dimethyl Phthalate should be included in the safety assessment as much of the published literature involves data on these ingredients together; however, the Panel stressed that any use, exposure, or risk data from one ingredient could not be read-across to the other ingredients in the report, citing in part very different use conditions from one ingredient to the next. The Panel also offered guidance on the presentation of the data, especially data relating to endocrine effect, in the updated safety assessment.

Additionally, the Panel discussed the current regulatory status of Dibutyl Phthalate in the European Union and in several US states. The Panel requested clarification on the status of these regulations, and the data that support such.

TO: Bart Heldreth Ph.D., Executive Director – Cosmetic Ingredient Review
Expert Panel for Cosmetic Ingredient Safety

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: May 6, 2024

SUBJECT: Margin of Exposure compared to Margin of Safety

The CIR Science and Support Committee (CIR SSC) encourages the inclusion of quantitative risk assessments in CIR reports on a case-by-case basis. We note that in the scientific literature the terms Margin of Safety (MoS) and Margin of Exposure (MoE) are often used interchangeably, which is incorrect[1]. We would like to explain the difference between these two terms so they can be used correctly in CIR reports.

Although the Scientific Committee for Consumer Safety (SCCS) uses the term Margin of Safety, they are calculating Margins of Exposure. Margins of Exposure take a point of departure (POD), e.g., a NOAEL from an animal study, and divide it by estimated human exposure. Typically, Margins of Exposure should be 100 or greater. This factor of 100 is to account for inter- and intra-species default extrapolation factors of 10X each.

MoE = POD/Human Exposure (typically MoE >100 is acceptable default)

In contrast, a Margin of Safety starts with a dose that is considered safe. The doses considered safe already incorporated uncertainty or extrapolation factors to account for inter- and intra-species differences and to account for duration of exposure. The doses considered safe include EPA reference doses and dietary acceptable daily intakes. A Margin of Safety calculation takes a value that has already been adjusted and is considered safe and divides it by estimated human exposure. Because the POD has already been adjusted with uncertainty or extrapolation factors to estimate a safe dose, a Margin of Safety ≥1 is acceptable.

MoS = (POD/UF)/Human Exposure (typically MoS >1 is acceptable)

[1] https://www.efsa.europa.eu/en/topics/topic/margin-exposure