ADMIN

Memo
Agenda
Minutes

EXPERT PANEL MEETING
September 11-12, 2023

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: 166th Meeting of the Expert Panel — Monday and Tuesday, September 11th - 12th, 2023
Date: August 18, 2023

Welcome to the third Panel Meeting of 2023! The agenda and accompanying materials for the 166th Expert Panel Meeting, to be held on September 11-12, 2023, are now available. This meeting will be held in-person at the Melrose Georgetown Hotel, 2430 Pennsylvania Avenue NW, Washington, DC 20037. We will have a virtual component to this in-person meeting; however, this component will be only of a spectator nature, and will not allow for any interaction with the Panel or Staff. If you are unable to attend in person and are interested in seeing the proceedings of the Panel, you may register to watch virtually, in advance of the meeting, at the meeting page:

https://www.cir-safety.org/meeting/166th-expert-panel-meeting

The meeting agenda includes the consideration of 9 reports advancing in the review process, including 6 final reports, 1 tentative report, and 2 draft reports. Also on the agenda are 8 rereview documents (6 proposals for rereview and 2 rereview summaries). ***In each case of a rereview proposal, the Panel is only being asked if the report should be reopened; in each case of a rereview summary, the Panel is only being asked to provide editorial comments.*** Additionally, there are 7 administrative documents, including a strategy memo for Toluene, a document on the dosage used in HRIPTs, a Hair Dye Epidemiology Resource Document for finalization and journal selection, guidance regarding nitrosation, FDA draft guidance regarding registration, guidance from EU authorities, and finalization of the 2024 Priorities.

Just for your information, while CIR was able to obtain updated frequency of use information earlier this year, the FDA VCRP has since come to an end. With the changes to be implemented as part of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), FDA has chosen to start afresh with a separate and distinct mandatory reporting program (estimated open for submissions in October).

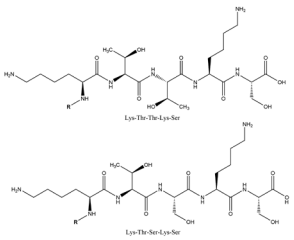
Also, in an attempt to reduce the quantity of late breaking information, we are making a cutoff for all information sent to the Panel. The exception to this cutoff is any pertinent information relevant to a Draft Final Report. ***Submissions received on non-final reports, after the issuance of the Wave 2 supplement on August 31, will be held back until the next iterations of those reports (e.g., a submission received on September 1 for the draft Pentapeptides report, will not be forwarded to the Panel until the next iteration is reviewed).***

Finally, Dr. Don Bjerke, Chair of the CIR Science and Support Committee, has agreed to deliver a presentation on dose per unit area of skin as an appropriate dose metric for skin sensitization, and on the use of new approach methodologies (NAMs), titled "Skin Sensitization Risk Assessment and Confidence in New Approach Methodologies."

Team Meetings

Draft Report - There are 2 draft reports for review. - Sufficient data to proceed, or issue an Insufficient Data Announcement (IDA)?

1. Pentapeptides – DR (Preethi) – ***Dr. Belsito reports on day 2*** – This is the first time the Expert Panel for Cosmetic Ingredient Safety (Panel) has seen a safety assessment of Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4. A Scientific Literature Review (SLR) was announced on April 18, 2023. Of note, data for two amino acid sequences of Palmitoyl Pentapeptide-4 have been included, namely palmitoyl-lysine-threonine-threonine-lysine-serine (Pal-KTTKS) and palmitoyl-lysine-threonine-serine-lysine-serine (Pal-KTSKS). Test article sequences have been indicated throughout the report.



   Palmitoyl Pentapeptide-4 was initially included as part of a 2013 Draft Report on the safety of Palmitoyl Oligopeptides. Subsequently, the Palmitoyl Oligopeptides nomenclature was retired from the *Dictionary*, and the Panel decided to reorganize and regroup these ingredients into separate reports based on shared amino acid sequence; accordingly, this ingredient family was formed. Data on Palmitoyl Pentapeptide-4 that were submitted for use in that 2013 draft report are now included in this package for your review.

   According to 2023 VCRP survey data, Palmitoyl Pentapeptide-4 has the greatest reported frequency of use; it is reported to be used in 239 formulations, 223 of which are leave-on products. Myristoyl Pentapeptide-4 is reported to have 4 uses, while Pentapeptide-4 has 1 reported use. The results of the concentration of use survey conducted by the Council in 2022 indicate Myristoyl Pentapeptide-4 has the highest maximum reported concentration of use, at up to 0.05% in other eye makeup preparations. The frequency of use of Palmitoyl Pentapeptide-4 has increased notably since 2012, at which time it was reported to the VCRP to be used in 51 formulations. The highest reported maximum concentration of use for Palmitoyl Pentapeptide-4 in 2013 was 0.00061% in eye lotions and face and neck preparations.

   Some of these ingredients are reported to be used in products that are applied near the eye; as stated above, Palmitoyl Pentapeptide-4 is used at up to 0.05% in eye makeup preparations. Palmitoyl Pentapeptide-4 is reported to be used in a face powder (concentration not provided) and could possibly be inhaled.

   Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not (***yet***) available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of 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.

   After reviewing these documents, 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 split conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

2. Charcoal – DR (Christina) – ***Dr. Cohen reports on day 2*** – This is the first time the Panel has seen a safety assessment of Charcoal, Charcoal Extract, Charcoal Powder, and Activated Charcoal. The SLR was issued by CIR on April 18, 2023. Activated Charcoal is not currently listed in the Dictionary; however, it is reported to be in use according to both the FDA VCRP database for frequency of use and the concentration of use survey conducted by the Council.

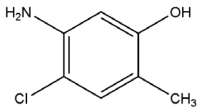
   According to 2023 VCRP survey data, Charcoal Powder has the highest frequency of use; it is reported to be used in 231 formulations, with a majority of uses in rinse-off formulations, such as skin cleansing preparations. Activated Charcoal is reported to be used in 53 formulations, also with the majority of uses in rinse-off formulations. The results of the concentration of use survey conducted

by the Council in 2021 indicate that Charcoal Powder has the highest concentration of use; it is used at up to 4.8% in eyeliners and up to 4% in paste masks (mud packs).

After reviewing these documents, 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 split 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?

1. 5-Amino-4-Chloro-*o*-Cresol – TAR (Christina) – ***Dr. Belsito reports on day 2*** – At the March 2023 meeting, the Panel determined that the data were insufficient to support safety of this hair dye ingredient. The additional data needs are:



   - Method of manufacture
   - Concentration of use for 5-Amino-4-Chloro-o-Cresol HCl

   Since the Insufficient Data Announcement (IDA) was issued, CIR received notice that 5-Amino-4-Chloro-o-Cresol HCl has no reported concentrations of use. The 2023 VCRP survey data report that there are no uses for either of these ingredients. These updates have been highlighted to aid the Panel's review. No other data have been received.

   A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider these items, discuss the data (or lack thereof), and issue a Tentative Amended Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

Draft Final Reports - There are 6 Draft Final Reports for consideration. - Review these drafts, especially the rationales provided in the Discussion sections, and issue these as Final Reports, as appropriate.

1. Olive – FR (Christina) – ***Dr. Belsito reports on day 2*** – At the June 2023 meeting, the Panel issued a Tentative Report with the conclusion that the following 16 *Olea europaea* (olive)-derived ingredients are safe in cosmetics in the present practice of use and concentration described in this safety assessment:

Hydrolyzed Olive Fruit	Olea Europaea (Olive) Fruit Water
Hydrolyzed Olive Fruit Extract	Olea Europaea (Olive) Husk Powder
Hydrolyzed Olive Leaf Extract	Olea Europaea (Olive) Leaf
Olea Europaea (Olive) Fruit	Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Fruit Extract	Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Fruit Juice	Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Fruit Juice Extract	Olea Europaea (Olive) Seed
Olea Europaea (Olive) Fruit Unsaponifiables	Olea Europaea (Olive) Seed Powder

   Additionally, the Panel also concluded that the available data are insufficient to make a determination of safety for the following 7 *Olea europaea* (olive)-derived ingredients under the intended conditions of use in cosmetic formulations:

Olea Europaea (Olive) Bark Extract	Olea Europaea (Olive) Flower Water
Olea Europaea (Olive) Branch Extract	Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Bud Extract	Olea Europaea (Olive) Wood Extract
Olea Europaea (Olive) Flower Extract	

   The additional data needed to determine the safety of these ingredients in cosmetics are:

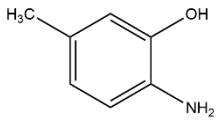
   - Method of manufacture for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch

Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract

- Composition and impurities data for Olea Europaea (Olive) Branch Extract and Olea Europaea (Olive) Flower Water
- 28-day dermal toxicity data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
    - If positive, additional data (e.g., DART and genotoxicity data) may be needed
- Dermal irritation and sensitization data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract

Since the June meeting, CIR has received no new unpublished data. After carefully reviewing the Abstract, Discussion, and Conclusion, the Panel should be prepared to issue a Final Report.

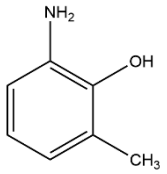
2. 6-Amino-*m*-Cresol – FAR (Christina) – ***Dr. Cohen reports on day 2*** – At the June 2023 meeting, the Panel issued a Tentative Amended Report with the conclusion that the available data are insufficient to make a determination of safety for 6-Amino-m-Cresol under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for this hair dye ingredient, the following additional data are needed:



    - Method of manufacture
    - In vivo genotoxicity studies

    Since the June meeting, CIR has received no new unpublished data. 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.

3. 6-Amino-*o*-Cresol – FAR (Christina) – ***Dr. Belsito reports on day 2*** – At the June 2023 meeting, the Panel issued a Tentative Amended Report with the conclusion that the available data are insufficient to make a determination of safety for 6-Amino-*o*-Cresol under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for this hair dye ingredient, the following additional data are needed:



    - Method of manufacture
    - Composition and impurities
    - Concentration of use
    - Absorption, distribution, metabolism, and excretion studies
        - If absorbed, developmental and reproductive toxicity studies, genotoxicity studies, and potentially other endpoints may be needed

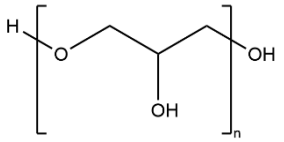
    Since the June meeting, CIR has received no new unpublished data. The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Amended Report.

4. *Zanthoxylum piperitum* – FR (Regina) – ***Dr. Cohen reports on day 2*** - At the June 2023 meeting, the Panel issued a Tentative Report for public comment with the conclusion that the 4 *Zanthoxylum piperitum*-derived ingredients named in this report are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing.

    No unpublished data were submitted since the issuing of the Tentative Report. At the June 2023

meeting the Panel considered additional published data that might be included in the report. It was decided that one additional study on *Zanthoxylum piperitum*-derived ingredients should be incorporated; those data consist of additional genotoxicity details and have been incorporated into this report. 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.

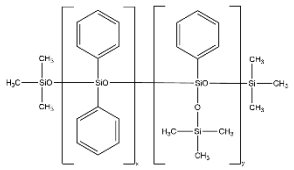
5. Polyglycerins – FR (Preethi) – ***Dr. Belsito reports on day 2*** - This is the second time the Panel has seen a safety assessment of these 4 cosmetic ingredients. At the June 2023 meeting, the Panel issued a Tentative Report for public comment with the conclusion that Diglycerin, and Polyglycerin-3, -6, and -10 are safe in cosmetics in the present practices of use and concentration described in the safety assessment.



In addition to discussing the robust toxicological profile, the Panel noted that these polyglycerins are likely to break down and exist as mixtures of varying lengths, including the monomer, glycerin. The Panel considered their prior safety determination of glycerin, with the conclusion that glycerin is safe as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment. Thus, the Panel reasoned that it would be appropriate to use data from the 2019 report on this monomer as read-across to address data gaps, specifically for repeated dose, developmental and reproductive toxicity, and carcinogenicity endpoints. Accordingly, summaries of these data have been incorporated into this report on polyglycerins. Please note, the safety of glycerin is not being reviewed in the report on polyglycerins; however, because it is used for read-across, the 2019 glycerin report has been included in this package for your use.

No new data were received. 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.

6. Phenyl-Substituted Methicones – FR (Preethi) – ***Dr. Cohen reports on day 2*** – This is the fourth time the Panel has seen a safety assessment of these 7 cosmetic ingredients. At the June 2023 meeting, the Panel issued a Tentative Report for public comment with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled.



The Panel identified the following data needs for these ingredients:

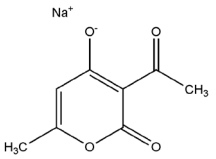
- Clarification of the identity and chemical nomenclature for the test article referred to as Phenyl Trimethicone in the SEHSC data submission
- Additional respiratory toxicity data at, or above, the reported maximum concentration of use in inhaled exposures near the face (Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    - Preferably, the protocol should be similar to the short-term inhalation toxicity study described in the original report (i.e., a 4-wk study in which rats were exposed twice daily to a 30-s burst of an aerosol containing 3% Phenyl Trimethicone, followed by a 15-min chamber exposure).

The SEHSC has informed CIR that upon being made aware that CAS No. 70131-69-0 is no longer associated in the Dictionary with the INCI name Phenyl Trimethicone, the data they submitted are not appropriate for inclusion in the report (i.e., the test article in their data submission comprised a polysilsesquioxane, not a phenyl-substituted methicone). Accordingly, these data have been removed from this Draft Final Report. No further data were received.

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report, and provide the editorial changes that should be made in the Discussion in response to receipt of the clarification from SEHSC. The Panel should then issue a Final Report.

Abbreviated Rereviews (i.e., rereview proposals) – There are 6 rereview documents – Because it has at least been 15 years since the previous reviews were published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, in each case, the Panel is only being asked if the report should be reopened.

1. Sodium Dehydroacetate – RR (Priya) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Sodium Dehydroacetate and Dehydroacetic Acid in 1985, with the conclusion that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration, as stated in that report. The Panel previously considered a re-review of this report in 2003 and re-affirmed the 1985 conclusion, as published in 2006.



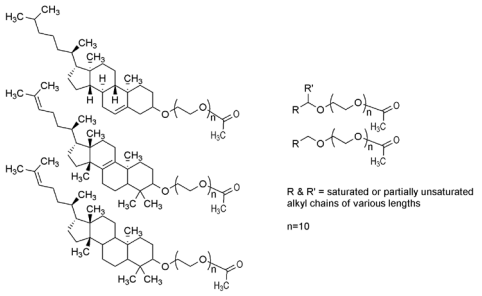
In July 2023, an extensive search of the world's literature was performed for studies dated 2000 forward. New studies were found for several relevant endpoints (e.g., absorption, distribution, metabolism, and excretion, acute oral toxicity, repeated-dose toxicity, developmental and reproductive toxicity, genotoxicity, dermal irritation, dermal sensitization, and ocular irritation). Of note, are hypersensitivity case reports of patients reporting adverse effects following use of creams containing Sodium Dehydroacetate (for ulcer treatment). In addition, one study was found suggesting the photoisomerization potential of Sodium Dehydroacetate and Dehydroacetic Acid.

Frequency of use of both Sodium Dehydroacetate and Dehydroacetic Acid have significantly increased according to 2023 FDA VCRP data. In 2002, Sodium Dehydroacetate and Dehydroacetic Acid were reported to be used in 325 and 88 formulations, respectively. In 2023, Sodium Dehydroacetate and Dehydroacetic Acid are reported to be used in 1233 and 833 formulations, respectively. The 2023 reported concentrations of use for both ingredients (maximum concentrations of 0.6% for Sodium Dehydroacetate and 0.7% for Dehydroacetic Acid) are the same maximum concentrations as reported in 2003.

According to the *Dictionary*, as in the original report, both ingredients are reported to function as preservatives in cosmetics. It should be noted that European Union regulations state that Sodium Dehydroacetate and Dehydroacetic Acid may be used as a preservative in cosmetics at up to 0.6% (as acid); however, these ingredients should not be used in aerosol dispensers (sprays; it is not indicated why these ingredients should not be used in sprays). Dehydroacetic Acid is reported to be used at 0.000008% in an aerosolized hair spray.

If upon review of the new studies and updated use data, the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, confirming the original conclusion, will be presented at an upcoming meeting.

2. Laneth-10 Acetate – RR (Priya) – ***Dr. Belsito reports on day 2*** – The Panel first published a review of the safety of Laneth-9 Acetate and Laneth-10 Acetate in 1982, with the conclusion that on the basis of the available animal data and limited human experience presented in the report, these ingredients are safe for topical applications to humans in the present practices of use and concentration. The Panel previously considered a re-review of this report in 2002 and re-affirmed the 1982 conclusion, as published in 2005. These two ingredients were originally reviewed with three other ingredients (Laneth-5, Laneth-16, and Laneth-25); however, these other three ingredients are not being reviewed herein as these ingredients were subsequently included in the Alkyl PEG Ethers report.



In July 2023, an extensive search of the world's literature was performed for studies dated 2000 forward. No relevant published data were found. In 2001, Laneth-10 Acetate was reported to be used according to the VCRP (44 uses), but concentration of use data were not reported. Additionally, no uses were reported for Laneth-9 Acetate in either the VCRP or the concentration of use survey. Currently, Laneth-9 Acetate and Laneth-10 Acetate have no reported uses, according to a 2022 concentration of use survey and 2023 FDA VCRP data. Because Laneth-9 Acetate had no previous (2001) or current (2022/2023) reported uses, it has not been included in the use table.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, confirming the original conclusion, will be presented at an upcoming meeting.

3. Acacia Senegal Gum Extract – RR (Regina) – ***Dr. Cohen reports on day 2*** –

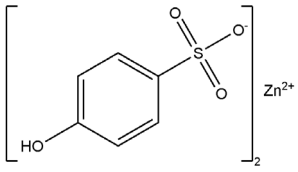
The Panel previously reviewed the safety of Acacia Senegal Gum and Acacia Senegal Gum Extract as part of a larger group of ingredients derived from the acacia plant. In 1998, the Panel initially issued a Final Report with an insufficient data conclusion for the entire group of acacia ingredients reviewed at that time, including Acacia Senegal Gum and Acacia Senegal Gum Extract. Subsequently, the Panel's data needs were met for only Acacia Senegal Gum and Acacia Senegal Gum Extract, and an Amended Final Report was published in 2005. At that time, the Panel concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe as used in cosmetic products. Please note, per CIR Procedures, that because the other ingredients included in the larger group had an insufficient data conclusion, they are not included in this rereview.

In June 2023, an extensive search of the world's literature was performed for studies dated 2000 forward. New non-cosmetic use data that consists of current European Union regulations regarding use as a food additive were identified. Data which cover reproductive toxicity and occupational case studies were also found and are included for review.

The frequency and concentration of use of Acacia Senegal Gum and Acacia Senegal Gum Extract has increased for both ingredients since the Amended Final Report was published in 2005, with significant increases noted for Acacia Senegal Gum. Acacia Senegal Gum is now reported to be used in 287 formulations at up to 26.7% in other oral hygiene products (this category of use was not previously reported), and therefore may be incidentally ingested; in 2001, it was reported to be used in 1 formulation and at up to 9%. Use in baby products is also now reported in the VCRP.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, confirming the original conclusion, will be presented at an upcoming meeting.

4. Zinc Phenolsulfonate – RR (Regina) – ***Dr. Belsito reports on day 2*** –



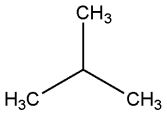
The Panel first published a review of the safety of Zinc Phenolsulfonate in 1986, with the conclusion that it is safe as a cosmetic ingredient in the present practices of use and concentration, as described in that safety assessment. The Panel previously considered a re-review of this report in 2004 and re-affirmed the 1986 conclusion, as published in 2006.

In July 2023, an extensive search of the world's literature was performed for studies dated 2001 forward. The Panel should note that in the European Union (EU), Zinc Phenolsulfonate is categorized in Annex III, the list of substances restricted in cosmetic substances. Current use in the EU is confined to deodorants, antiperspirants, and astringent lotions at a maximum concentration of 6%. Additionally, according to US 21CFR 310.545, there are inadequate data to establish general recognition of the safety and effectiveness of Zinc Phenolsulfonate in OTC drug products.

The frequency and concentration of use of Zinc Phenolsulfonate have decreased since this ingredient was last considered for re-review. According to 2023 frequency of use and concentration of use data, Zinc Phenolsulfonate is used in 1 formulation at up to 1% in leave-on products; in 2002, it was reported to be used in 23 formulations, and according to 2004 concentration of use data, at up to 4% in leave-on products.

If upon review of the new data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, confirming the original conclusion, will be presented at an upcoming meeting.

5. Isobutane – RR (Regina) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Isobutane, Isopentane, n-Butane, and Propane in 1982, with the conclusion that these ingredients are considered safe as cosmetic ingredients under present conditions of concentration and use, as described in that safety assessment. The Panel previously considered a rereview of this report in 2002 and re-affirmed the 1982 conclusion, as published in 2005.

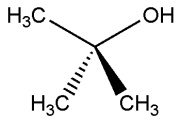


In July 2023, an extensive search of the world's literature was performed for studies dated 2000 forward. Current European Union regulations, toxicokinetic, toxicological, genotoxicity, developmental and reproductive toxicity, and irritation and sensitization studies, as well as case reports, were located and included for the Panel's consideration. Occupational exposure guidelines from The National Institute of Occupational Safety and Health for Isobutane, n-Butane, and Propane have also been included for the Panel's review.

The frequency and concentrations of use have increased for all of these ingredients since the rereview was published in 2005. According to 2023 frequency of use and 2022 concentration of use data, Isobutane is used in 392 formulations and at up to 98% nail products; in 2001, it was reported to be used in 338 formulations and at up to 83% in powder products. The Panel should also note that many of the reported use concentrations for each ingredient are for spray formulations (as these are propellants), and shampoo (non-coloring) preparations are now reported for all four ingredients.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, confirming the original conclusion, will be presented at an upcoming meeting.

6. *t*-Butyl Alcohol – RR (Preethi) – ***Dr. Belsito reports on day 2*** – The Panel first published a safety assessment of *t*-Butyl Alcohol in 1989, in which the Panel concluded the data were insufficient to support the safety of this ingredient in cosmetics. Subsequently, data were received that addressed the insufficiencies, and the Panel published an Amended Final Report of the Safety Assessment of *t*-Butyl Alcohol as Used in Cosmetics in 2005. On the basis of available animal and clinical data in that report, the Panel concluded that *t*-Butyl Alcohol is safe as used in cosmetic products.



In July 2023, an extensive search of the world's literature was performed for studies dated 2000 forward. Notable new information includes data on dermal absorption, toxicokinetics (in vivo and modeled), oral developmental and reproductive toxicity, in vitro genotoxicity, a guinea pig maximization test, species-specific effects on renal tumor induction, endocrine effects, and systemic/margin of exposure calculations. These newly found data appear to be merely cumulative, without any substantive differences when compared to that found in previous iterations of the report.

According to 2023 FDA VCRP data, *t*-Butyl Alcohol use has increased to 136 uses, from 32 reported uses in 1998. New reported uses include use in a baby product, in non-coloring hair products, and in products that come in contact with mucous membranes. Reported concentrations of use have increased; for example, the maximum reported use concentration for *t*-Butyl Alcohol in products which come in contact with mucous membranes increased from 0.0001% in bath soaps and detergents to 0.16% in other personal cleanliness products. In 2022, the maximum reported concentration of use for *t*-Butyl Alcohol was 0.91% in aftershave lotions, while in 1999, *t*-Butyl Alcohol was reported to be used at a maximum concentration of 0.5% in hair spray aerosol fixatives.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, confirming the original conclusion, will be presented at an upcoming meeting.

Administrative Items - there are 2 rereview summaries (presented in 1 book), 1 strategy memo, and 6 other administrative items.

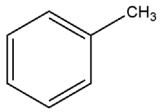
RRsums - The Panel is being asked for editorial comment.

1. Benzaldehyde – RRsum – (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

2. Polyquaternium-11 – RRsum – (Regina) – ***Dr. Belsito reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

SM – The Panel is being asked for guidance in regard to a strategy

3. Toluene – SM – (Priya||Jinqiu) – ***Dr. Cohen reports on day 2*** – Priya and Jinqiu have prepared a strategy to tackle the copious relevant data for Toluene. ***Would the Panel approve of this approach for screening the literature? If this does not align with their thinking, guidance is requested from the Panel on how to structure and present such an extensive array of studies.***



Other Admin

4. Dermal Dose in HRIPTs vs Product Usage – Admin (Jinqiu) – ***Dr. Belsito reports on day 2*** – The CIR Science and Support Committee (SSC) submitted a "Comparison of Ingredient Concentrations Tested in HRIPTs to Product Usage," dated July 11, 2023. Correspondingly, Dr. Don Bjerke, Procter & Gamble, Chair of the CIR SSC, will be presenting to the Panel on the morning of the first day of the meeting (September 11) on this subject, and on building confidence in NAMs.

   Upon consideration of the case example highlighted in the submission, what is the opinion of the Panel? Is an HRIPT at the maximum reported product use concentration always needed if the dose per unit area in an HRIPT of another tested product is greater than or equal to the dose per unit area following consumer exposure? Also, should all future CIR reports have a formal risk assessment section, to further confidence in methodologies?

5. Hair Dye EpidemiolgyResource Document – Admin (Jinqiu) – ***Dr. Cohen reports on day 2*** – At the March 2023 meeting, the Panel reviewed the updates on the Hair Dye Epidemiology Resource Document and maintained the conclusion that the currently available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer.

   The Panel also proposed that, after making some editorial changes, the document should be submitted to a journal specializing in epidemiology for publication. Accordingly, the document has been modified. In addition, an Abstract and Discussion have been prepared and incorporated, in anticipation of publication in a journal.

   The Panel should review this Document, taking into consideration whether the newly added sections are necessary for the final version that will replace the current one posted on CIR's Findings & Resources Documents page (https://www.cir-safety.org/cir-findings). ***If the Document is not deemed fit for finalization, any specific requirements or modifications needed should be clearly indicated. Jinqiu has also provided a number of potential epidemiology journals to submit the article to; the Panel is being asked to rank their preferences.***

6. FDA Nitrosation Impurities Guidance – Admin (Jinqiu) - ***Dr. Belsito reports on day 2*** – In August 2023, the US FDA Center for Drug Evaluation and Research (CDER) released the "Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) Guidance for Industry." The guidance was issued for immediate implementation in accordance with 21 CFR 10.115(g)(2). The FDA determined the information in the guidance was important for manufacturers and applicants of prescription and over-the-counter drugs with regards to recommended acceptable intake (AI) limits for NDSRIs that have been identified in many drug products and may be present in active pharmaceutical ingredients. If a potential risk for a nitrosamine impurity has been identified and validated by subsequent confirmatory testing, the FDA recommends the manufacturer or applicant develop an appropriate control strategy to ensure that the nitrosamine level remains at or falls below the AI limit.

   The Panel may want to consider whether the approach to predict carcinogenic potency categorization, as proposed in this Guidance document, along with the methodology for AI limits determination that uses

structural features of NDSRIs, can be utilized and incorporated into CIR safety assessments.

The CIR is working to bring Nitrosamine Resource Document to the Panel table in December. Dr. Ron Shank has agreed to provide his expert input therein. ***What influence should the Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities Guidance for Industry have on the Nitrosamine Resource Document?***

7. FDA Cosmetic Registration Draft Guidance – Admin (Christina) – ***Dr. Cohen reports on day 2*** – In August 2023, the US FDA Office of Cosmetics and Colors distributed for comment a draft of the "Registration and Listing of Cosmetic Product Facilities and Products: Guidance for Industry." This guidance is being developed in response to MoCRA and is open to public comments for consideration by the FDA. Included in this guidance is the proposed updated cosmetic product categories and codes (Appendix A). Previously, reporting use was voluntary (i.e., the now defunct VCRP); in accordance with MoCRA, reporting will be mandatory, and the updated categories will be utilized in the new mandatory cosmetic registration process.

   The new proposed categories have expanded some areas of information that the Panel has expressed a need for in the past (e.g., airbrush application is a sub-category for some makeup and indoor tanning preparations, and there is designation of leave-on and rinse-off for products that may have either type of use). Additionally, there are entirely new product categories, including children's eye makeup preparations, makeup preparations for children (not eye), and tattoo preparations. Finally, some product categories have been deleted or consolidated (e.g., fragrance sachets have been deleted and blushers and rouges have been combined).

   Upon review, does the Panel have any comments for the FDA on these product categories and suggestions for expansions? For example:
   - ***Are there any other product subcategories where it would be useful to know if there is a potential airbrush application?***
   - ***Should there be subcategories for aerosol or powder use that should be identified (e.g., dry shampoos, hair tonics, etc.)?***
   - ***Are there any categories or subcategories that the current list does not entail, but the Panel feels it should?***

   Any comments and suggestions the Panel has on the proposed product categories will be provided to the FDA following the September Panel meeting.

8. SCCS Notes of Guidance – Admin (Christina) – ***Dr. Belsito reports on day 2*** – In May 2023, the European Commission Scientific Committee on Consumer Safety (SCCS) issued the "SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation" (12th revision). The guidance reviews the current permissible methodologies of testing the SCCS uses to evaluate the safety of cosmetic ingredients. The SCCS updates the guidance regularly and considers it to be a living document. This document supersedes the Notes of Guidance from 2021.

   The revisions and updates to the current guidance include:
   - Updates to animal-free alternative methods such as new approach methodology (NAM); new in vitro genotoxicity testing methods; changes introduced to acute inhalation and skin irritation (e.g., the MucilAirTM model and air liquid interface (ALI) models); eyes irritation testing with DAL (Defined Approach for eye irritation, Liquid); and Defined Approaches for Skin Sensitization (DASS).
   - Updates to in silico prediction possibilities.
   - Discussion of the implementation of Next-Generation Risk Assessment (NGRA) and other approaches for assessing cosmetic safety, with definition of concepts such as

Bioactivity/Exposure Ratio (BER) and internal Threshold of Toxicological Concern (iTTC).
- Exposure of children to different cosmetic product categories according to age.
- Considerations for reviewing complex mixtures, botanicals, nanomaterials, and endocrine disruptors.

Upon review of the updated Notes of Guidance, which the SCCS uses to create their opinions, does the Panel see any endpoints or approaches CIR does not currently include in safety assessments that would be useful to the Panel's review of cosmetic ingredients or that would help strengthen the conclusions of the Panel?

9. 2024 Final Priorities – Admin (Bart) – ***Dr. Cohen reports on day 2*** – The CIR Procedures require preparation of the 2024 Draft Priority List for public comment by June 1, 2023. This list was provided to the Panel and reviewed at the March 2023 meeting; comments made at the March and June meetings have been considered and incorporated into this 2024 Draft Final Priority List.

   While the priority list includes only the lead ingredients, groupings of ingredients, drafted by CIR Staff, can be found on the following pages in the document. There are 18 reports proposed, covering 31 ingredients, on the 2024 Draft Final Priorities List. ***The Panel should finalize the 2024 Priorities at this meeting.***

Full Panel Meeting

The Panel will consider the 6 reports to potentially be issued as Final Reports, followed by the remaining reports advancing in the process (including the Tentative Report and Draft Reports). In addition, a consensus should be reached for the 6 rereview documents, the 2 rereview summaries, and the 7 other administrative items.

Please remember, the meeting starts at 8:30 am on day 1 and day 2. It is likely that the full Panel session will conclude before noon on day 2.

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

Agenda
166th Meeting of the Expert Panel for Cosmetic Ingredient Safety
September 11th – 12th, 2023

Monday, September 11, 2023

8:30 AM	**WELCOME TO THE 166th EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:45 AM	**PRESENTATION – Skin Sensitization Risk Assessment and Confidence in New Approach Methodologies**	**Dr. Don Bjerke (P&G; Chair of the CIR SSC)**
9:45 AM	**TEAM MEETINGS**	**Drs. Belsito/Cohen**

Dr. Belsito's Team*	
FR (CB)	Olive
FAR (CB)	6-Amino-*m*-Cresol
FAR (CB)	6-Amino-*o*-Cresol
TAR (CB)	5-Amino-4-Chloro-*o*-Cresol
DR (CB)	Charcoal
Admin (CB|BH|MF)	FDA Draft Guidance
Admin (CB|BH|MF)	SCCS NoG
FR (PR)	Phenyl-Substituted Methicones
FR (PR)	Polyglycerins
DR (PR)	Pentapeptides
RR (PR)	*t*-Butyl Alcohol
RRsum (MF|BH)	RR Summaries (all)
Admin (BH|MF)	Priorities
Admin (JZ|BH|MF)	Dermal Dose
Admin (JZ)	Nitrosation Impurities
Admin (JZ)	Hair Dye Epi
SM (PC|JZ)	Toluene
RR (PC)	Sodium Dehydroacetate
RR (PC)	Laneth-10 Acetate
FR (RT)	*Zanthoxylum piperitum*
RR (RT)	Acacia
RR (RT)	Isobutane
RR (RT)	Zinc Phenolsulfonate

Dr. Cohen's Team	
Admin (JZ|BH|MF)	Dermal Dose
Admin (JZ)	Nitrosation Impurities
Admin (JZ)	Hair Dye Epi
SM (PC|JZ)	Toluene
RR (PC)	Sodium Dehydroacetate
RR (PC)	Laneth-10 Acetate
FR (RT)	*Zanthoxylum piperitum*
RR (RT)	Acacia
RR (RT)	Isobutane
RR (RT)	Zinc Phenolsulfonate
RRsum (MF|BH)	RR Summaries (all)
Admin (BH|MF)	Priorities
FR (CB)	Olive
FAR (CB)	6-Amino-*m*-Cresol
FAR (CB)	6-Amino-*o*-Cresol
TAR (CB)	5-Amino-4-Chloro-*o*-Cresol
DR (CB)	Charcoal
Admin (CB|BH|MF)	FDA Draft Guidance
Admin (CB|BH|MF)	SCCS NoG
FR (PR)	Phenyl-Substituted Methicones
FR (PR)	Polyglycerins
DR (PR)	Pentapeptides
RR (PR)	*t*-Butyl Alcohol

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 || PR: Preethi Raj || RT: Regina Tucker || JZ: Jinqiu Zhu

*Team moves to the breakout room.

Tuesday, September 12, 2023			
8:30 AM	**WELCOME TO THE 166th FULL EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:40 AM	Admin	**MINUTES OF THE JUNE 2023 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 AM	**DIRECTOR'S REPORT**		**Dr. Heldreth**
9:10 AM	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**		
	Final Reports		
	FR (CB)	Olive - *Olea europaea*-derived ingredients - ***Dr. Belsito reports***	
	FAR (CB)	6-Amino-*m*-Cresol– ***Dr. Cohen reports***	
	FAR (CB)	6-Amino-*o*-Cresol – ***Dr. Belsito reports***	
	FR (RT)	*Zanthoxylum piperitum*-derived ingredients – ***Dr. Cohen reports***	
	FR (PR)	Polyglycerins – ***Dr. Belsito reports***	
	FR (PR)	Phenyl-Substituted Methicones – ***Dr. Cohen reports***	
	Reports Advancing		
	DR (PR)	Pentapeptide ingredients – ***Dr. Belsito reports***	
	DR (CB)	Charcoal ingredients – ***Dr. Cohen reports***	
	TAR (CB)	5-Amino-4-Chloro-*o*-Cresol ***– Dr. Belsito reports***	
	Other Items		
	RR (PC)	Sodium Dehydroacetate – ***Dr. Cohen reports***	
	RR (PC)	Laneth-10 Acetate – ***Dr. Belsito reports***	
	RR (RT)	Acacia Senegal Gum Extract – ***Dr. Cohen reports***	
	RR (RT)	Zinc Phenolsulfonate – ***Dr. Belsito reports***	
	RR (RT)	Isobutane – ***Dr. Cohen reports***	
	RR (PR)	*t*-Butyl Alcohol – ***Dr. Belsito reports***	
	RRsum (PR|BH|MF)	Benzaldehyde – ***Dr. Cohen reports***	
	RRsum (RT|BH|MF)	Polyquaternium-11 – ***Dr. Belsito reports***	
	SM (PC|JZ)	Toluene – ***Dr. Cohen reports***	
	Admin (JZ|BH|MF)	Dermal Dose in HRIPTs vs Product Usage – ***Dr. Belsito reports***	
	Admin (JZ)	Hair Dye Epidemiology Resource Document – ***Dr. Cohen reports***	
	Admin (JZ)	FDA Nitrosation Impurities Guidance – ***Dr. Belsito reports***	
	Admin (CB|BH|MF)	FDA Cosmetic Registration Draft Guidance – ***Dr. Cohen reports***	
	Admin (CB|BH|MF)	SCCS Notes of Guidance – ***Dr. Belsito reports***	
	Admin (BH)	2024 Final Priorities – ***Dr. Cohen reports***	

ADJOURN – *The next will be held virtually on Monday and Tuesday,* ***December 4 - 5, 2023****. 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 || PR: Preethi Raj || RT: Regina Tucker || JZ: Jinqiu Zhu

ONE HUNDRED SIXTY-FIFTH MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

June 12-13, 2023

Melrose Hotel, 2430 Pennsylvania Ave, NW, Washington DC

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

Linda Katz, M.D., M.P.H.

Prashiela Manga, 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

Regina Tucker, MS –Scientific Analyst

Information Services
Kevin Stone Fries, MLS - Information Services Manager

Other Meeting Attendees

Name	*Organization*
Yunqi An (virtual)	Victoria's Secret
Jay Ansell	Personal Care Products Council
Valentine Anyaibe (virtual)	Enhanced Compliance, Inc.
John Bailey	EAS
Don Bjerke	Procter & Gamble
Sharon Blinkoff	Locke Lord LLP
Deborah Church (virtual)	Catalyst Clinical Research, LLC
Sara Eglitis (virtual)	Enhanced Compliance, Inc.
Carol Eisenmann	Personal Care Products Council
Linda Giles	Transcription, Etc.
Arun Govindarajan (virtual)	unidentified
Jessica Madrigal (virtual)	unidentified
Nathaniel Minton (virtual)	Eastman Chemical Co.
Jeff Nicolo	Procter & Gamble
Joanne Nikitakis	Personal Care Products Council
Kimberly Norman	Personal Care Products Council
Alexandra Peterson	Personal Care Products Council
Audrey Pokrzywa	SILAB
Alexandra Gorman Scranton (virtual)	Women's Voices for the Earth
Daisy Shelton (virtual)	Eastman Chemical Co.
Prajakta Shimpi (virtual)	L'Oreal USA
Liz Toledo (virtual)	unidentified
Brian Wall (virtual)	Colgate-Palmolive
Janet Zang	US FDA

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 165th meeting of the Expert Panel for Cosmetic Ingredient Safety. The Panel reviewed 21 documents, including 3 final reports, 5 tentative reports, and 5 draft reports. Dr. Bergfeld acknowledged all the work put forth by the CIR staff and directors, the CIR Science and Support Committee, and the Panel to prepare for this meeting.

Dr. Bergfeld noted the comments received from outside parties, including the Women's Voice for the Earth.

Dr. Bergfeld also noted that among the items the Panel would be reviewing are boilerplates and the Nitrosation Resource Draft Document. She thanked Ms. Fiume and Mr. Zhu for their work on these items. Lastly, the Panel would be considering requests from the FDA regarding the 2024 Priority List.

APPROVAL OF MINUTES

The minutes of the March 6-7, 2023 (164th) Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth thanked the liaisons to the Expert Panel for Cosmetic Ingredient Safety. In the mid 1970's, representatives from the Council (then Cosmetics, Toiletries, and Fragrance Association), the FDA, and the Consumer Federation of America, sat down to discuss cosmetics safety and the protection of consumers, resulting in the formation of CIR, and representatives from each of these entities participate in every meeting of the Panel, adding so much to the process. Dr. Heldreth also thanked the CIR staff, the Expert Panel, the CIR Science and Support Committee, and all other participants.

FINAL SAFETY ASSESSMENTS

5-Amino-6-Chloro-*o*-Cresol

The Panel issued a Final Amended Report with the conclusion that 5-Amino-6-Chloro-*o*-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.

5-Amino-6-Chloro-*o*-Cresol is reported to function as a semi-permanent and 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 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 5-Amino-6-Chloro-*o*-Cresol absorbs slowly through the skin, is not genotoxic, and has a reported low concentration of use of up to 0.24% in hair dyes. The Panel considered these findings, coupled with the short exposure time as a rinse-off product, and determined that the data are sufficient to determine the safety of 5-Amino-6-Chloro-*o*-Cresol for use as a hair dye ingredient.

Hyaluronates

The Panel issued a Final Report with the conclusion that the following 7 hyaluronates are safe as used in the present practices of use and concentration as described in the safety assessment.

Hyaluronic Acid‡
Hydrolyzed Calcium Hyaluronate
Hydrolyzed Hyaluronic Acid
Hydrolyzed Sodium Hyaluronate
Potassium Hyaluronate‡
Sodium Acetylated Hyaluronate
Sodium Hyaluronate‡

‡previously reviewed by the Panel

Three of these ingredients were previously reviewed by the Panel in a safety assessment published in 2009 and were considered safe in the present practices of use and concentration, as described in the 2009 safety assessment.

The safety of all 7 ingredients was supported by available toxicity data, the presence of Hyaluronic Acid as an endogenous substance in the skin, and the extensive use of these ingredients without reported adverse effects. Although sensitization data at maximum reported use concentrations were not available, the need for such studies was mitigated by the fact these ingredients have large molecular weights (and as such, are not expected to absorb into the skin), and because although these ingredients are widely utilized, there are a lack of case reports following topical application.

The Panel was concerned with the risks inherent in using animal-derived ingredients (i.e., rooster combs), namely the transmission of infectious agents and biologically-derived impurities (e.g., nucleic acids, proteins, endotoxins). The Panel stressed that the cosmetics industry should continue to use the necessary procedures to sufficiently limit detectible pathogenic viruses, infectious agents, and/or biologically-derived impurities.

Phytosteryl Glutamates

The Panel issued a Final Report with the conclusion that the following 3 phytosteryl glutamates are safe in cosmetics in the present practices of use and concentration as described in the safety assessment.

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate
Phytosteryl/Behenyl/ Octyldodecyl/Isostearyl Lauroyl Glutamate

Phytosteryl/Octyldodecyl Lauroyl Glutamate

The Panel noted the lack of confirmatory sensitization data at maximum reported concentrations of use; however, this need was mitigated by the negative guinea pig maximization assays performed on the phytosteryl glutamates that included epidermal induction and challenge at 100%. The Panel also considered the robust data profile, which included 28-d oral toxicity studies with a lack of test-substance related toxicity and negative mutagenicity studies. Developmental and reproductive toxicity (DART) data are lacking; however, these ingredients are not expected to be absorbed, thereby mitigating concern. The Panel discussed the plant steroid sitosterol and the possible biological effects when it interacts with different receptors in the body; mutations in ATP-binding cassette (ABC) transporters have been shown to lead to the accumulation of plant sterols causing the disorder sitosterolemia.

TENTATIVE SAFETY ASSESSMENTS

6-Amino-*m*-Cresol

The Panel issued a Tentative Amended Report for public comment with the conclusion that the available data are insufficient to make a determination of safety for 6-Amino-*m*-Cresol under the intended conditions of use in hair dye formulations. The Panel determined that the data needs from the original Insufficient Data Announcement (IDA) issued following the December 2022 Panel meeting remain unmet. In order to come to a conclusion of safety for this hair dye, the following data are needed:

- Method of manufacture
- in vivo genotoxicity studies

6-Amino-*o*-Cresol

The Panel issued a Tentative Amended Report for public comment with the conclusion that the available data are insufficient to make a determination of safety for 6-Amino-*o*-Cresol under the intended conditions of use in hair dye formulations. The Panel determined that the data needs from the original IDA issued following the December 2022 Panel meeting remain unmet. In order to come to a conclusion of safety for this hair dye, the following additional data are needed:

- Method of manufacture
- Composition and impurities
- Concentration of use
- Absorption, distribution, metabolism, and excretion (ADME) studies
    - If absorbed, additional data (e.g., DART and genotoxicity data) may be needed

***Olea europaea* (Olive)-derived ingredients**

The Panel issued a Tentative Report for public comment with the conclusion that the following 16 *Olea europaea* (olive)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Hydrolyzed Olive Fruit*	Olea Europaea (Olive) Fruit Water*
Hydrolyzed Olive Fruit Extract*	Olea Europaea (Olive) Husk Powder*
Hydrolyzed Olive Leaf Extract*	Olea Europaea (Olive) Leaf*
Olea Europaea (Olive) Fruit	Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Fruit Extract	Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Fruit Juice*	Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Fruit Juice Extract*	Olea Europaea (Olive) Seed*
Olea Europaea (Olive) Fruit Unsaponifiables	Olea Europaea (Olive) Seed Powder

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

Additionally, the Panel also concluded that the available data are insufficient to make a determination of safety for the following 7 *Olea europaea* (olive)-derived ingredients under the intended conditions of use in cosmetic formulations:

Olea Europaea (Olive) Bark Extract**	Olea Europaea (Olive) Flower Water**
Olea Europaea (Olive) Branch Extract**	Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Bud Extract	Olea Europaea (Olive) Wood Extract**
Olea Europaea (Olive) Flower Extract**	

***There are currently no uses reported for these ingredients.*

To come to a conclusion of safety for these 7 cosmetic ingredients, the following additional data are needed:

- Method of manufacture for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
- Composition and impurities data for Olea Europaea (Olive) Branch Extract and Olea Europaea (Olive) Flower Water
- 28-day dermal toxicity data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
    - If positive, additional data (e.g., DART and genotoxicity data) may be needed
- Dermal irritation and confirmatory sensitization data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract

Phenyl-Substituted Methicones

The Panel issued a Tentative Report for public comment with a mixed conclusion for these 7 phenyl-substituted methicone ingredients. Specifically, the Panel concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled:

Diphenyl Dimethicone	Phenyl Methicone
Diphenylsiloxy Phenyl Trimethicone	Phenyl Trimethicone
Diphenylsiloxy Phenyl/Propyl Trimethicone	Trimethylsiloxyphenyl Dimethicone
Phenyl Dimethicone	

The Panel considered data received in response to the IDA issued at the March 2023 meeting, including correspondence from the Silicones, Environmental, Health, and Safety Center (SEHSC) and a CAS number review for Phenyl Trimethicone conducted by the Personal Care Products Council (Council). The Panel acknowledged that the SEHSC stated the data set they submitted can be considered representative data on Phenyl Trimethicone. However, the test article in those studies was associated with CAS No. 70131-69-0, which is no longer associated with Phenyl Trimethicone in the wINCI *Dictionary*. Therefore, it was still unclear to the Panel as to whether data submitted for the test article under the name Phenyl Trimethicone, but with CAS No. 70131-69-0, refer to the ingredient included in this report, and if they are applicable to this safety assessment.

Furthermore, the Panel agreed that data on intermittent short-term inhalation exposure and on the particle size distribution and concentrations of use for these ingredients in products which may be incidentally inhaled are also lacking. Accordingly, the additional data needs are:

- Clarification of the identity and chemical nomenclature for the test article referred to as Phenyl Trimethicone in the SEHSC data submission
- Additional respiratory toxicity data at, or above, the reported maximum concentration of use in inhaled exposures near the face (Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    - Preferably, the protocol should be similar to the short-term inhalation toxicity study described in the original report (rats were exposed to a 30-s burst, followed by a 15-min chamber exposure to an aerosol containing 3% Phenyl Trimethicone).

Polyglycerins

The Panel issued a Tentative Report for public comment with the conclusion that the following 4 ingredients are safe as used in the present practices of use and concentration described in the safety assessment:

Diglycerin	Polyglycerin-6
Polyglycerin-3	Polyglycerin-10

According to 2023 Voluntary Cosmetic Registration Program data and results from concentration of use survey data obtained by Council in 2022, Diglycerin and Polglycerin-3 have 222 and 221 reported uses, respectively, and Diglycerin is used at up to 28% in skin cleansing products, with a maximum reported leave-on dermal concentration of 5% in face and neck products. The Panel considered their prior safety determination of glycerin in 2019 and reasoned that it would be appropriate to use data on this monomer as read-across for repeated oral dose and DART endpoints. Negative genotoxicity data mitigated the need for carcinogenicity data. Additionally, the Panel discussed the otherwise robust toxicological profile, including negative dermal irritation and sensitization data.

***Zanthoxylum piperitum*-derived ingredients**

The Panel issued a Tentative Report for public comment with the conclusion that the following 4 *Zanthoxylum piperitum*-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing:

Zanthoxylum Piperitum Fruit Extract	Zanthoxylum Piperitum Peel Extract
Zanthoxylum Piperitum Oil*	Zanthoxylum Piperitum Peel Water*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

The Panel noted that *Zanthoxylum piperitum* extract is classified as generally recognized as safe (GRAS) and considered its GRAS status to mitigate concerns for systemic toxicity. Additionally, these ingredients are not expected to absorb through the skin and have low reported maximum concentrations of use (i.e., 0.01%). The Panel also discussed the presence of potential sensitizers (e.g., citronellol and geranial acetate) in *Zanthoxylum piperitum*-derived ingredients. Because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Accordingly, the Panel concluded the ingredient should be formulated to be non-sensitizing in cosmetic formulations.

INSUFFICIENT DATA ANNOUNCEMENTS

MIBK

The Panel issued an IDA for MIBK. The additional data needed to determine safety for this cosmetic ingredient are:

- Concentration of use and function in aftershave formulations
- Confirmatory sensitization studies at maximum use concentration

Prostaglandin Analogues

The Panel issued an IDA for Ethyl Tafluprostamide and Isopropyl Cloprostenate. The additional data needed to determine safety for these ingredients are:

- Concentration of use data on both Ethyl Tafluprostamide and Isopropyl Cloprostenate (percentage of ingredients in marketed cosmetic products)
- Information on packaging and directions for consumer use (particular emphasis placed on how packaging/directions prevent ocular exposure)
- 28-d dermal toxicity assay on both Ethyl Tafluprostamide and Isopropyl Cloprostenate
    - if positive, other toxicity endpoints necessary (e.g., genotoxicity, DART) may be needed
- Inhibition constant (K_i) data on the binding affinity of Ethyl Tafluprostamide and Isopropyl Cloprostenate on relevant PGF2α receptors, as compared to K_i values for bimatoprost (Food and Drug Administration (FDA)-approved prostaglandin analogue used for treatment of glaucoma)
- Irritation and confirmatory dermal sensitization on Ethyl Tafluprostamide and Isopropyl Cloprostenate at maximum concentrations of use (pending receipt of concentration data for both ingredients)
- Determination of intraocular pressure assay following use of an eyelash preparation containing Isopropyl Cloprostenate (when applied as a cosmetic (to eyelashes))

The Panel is aware that multiple studies on Ethyl Tafluprostamide on various endpoints (e.g., dermal penetration, dermal sensitization) are currently being performed and will soon be submitted by industry. The Panel will consider these data, once received.

Yeast ingredients

The Panel evaluated the Revised Draft Report on 56 yeast-derived ingredients and issued an IDA. The additional data needed to determine safety for this cosmetic ingredient are:

- confirmatory dermal sensitization data and data on food use/GRAS status on the yeast species used to derive these ingredients for all ingredients in which this is absent
    - in lieu of food use/GRAS status data, 28-d dermal toxicity data may be considered.

Currently, ingredients with both clinical dermal sensitization data and food use/GRAS status include Hydrolyzed Metschnikowia Agaves Extract, Metschnikowia Agaves Extract, and Pichia Anomala Extract; accordingly, no further data is needed on these three ingredients in order to determine safety.

The Panel discussed the addition of Qualified Presumption of Safety (QPS) status (as designated by the European Union) of these yeast species, along with clarification on the meaning of a QPS status.

TABLED

Fatty Amphocarboxylates

The Panel evaluated the Draft Report on 11 fatty amphocarboxylates, along with a large data submission on this ingredient group submitted to the Panel in June 2023, and determined that this report should be tabled for incorporation of all submitted data into the report. In addition, the Panel requested the following data:

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

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 5 previous assessments for re-review. The Panel determined that the following 3 reports should be reopened; a Draft Amended Report will be presented to the Panel for each of these safety assessments at a later meeting.

- BHA – 1 ingredient
- Lanolin-derived ingredients – 9 ingredients
- Octoxynols – 25 ingredients

In contrast, the Panel reaffirmed the conclusions reached for the following 2 safety assessments (choosing to not re-open the original reports). A re-review summary will be presented to the Panel for each of these safety assessments at an upcoming meeting.

- Benzaldehyde – 1 ingredient
- Polyquaternium-11– 1 ingredient

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 3 re-review summaries:

- Dioscorea Villosa (Wild Yam) Root Extract – 1 ingredient
- Polyamino Sugar Condensate – 1 ingredient
- Prunus Amygdalus Dulcis (Sweet Almond) Seed Meal – 1 ingredient

2024 PRIORITIES REQUEST

Following the March 2023 discussion of the draft 2024 Priorities List, CIR received communication from members of the FDA nominating ingredient additions to the 2024 Priority List, for-cause. Specifically, the FDA nominated Toluene (last considered in 2006) and Dibutyl Phthalate (last considered in 2017) for accelerated re-reviews, and Trimethylbenzoyl Diphenylphosphine Oxide for first-time review prioritization. The Panel agreed to these requests. Draft Amended Reports will be prepared for Toluene and Dibutyl Phthalate for review at future meetings, and review of Trimethylbenzoyl Diphenylphosphine Oxide will be prioritized.

NITROSATION RESOURCE DOCUMENT

The Panel reviewed the Nitrosation Resource Document, making relevant comments and edits. The Panel requested the document be further reviewed and revised by an outside professional who has expertise on the toxicity of *N*-nitroso compounds and *N*-nitrosation pathways. This document will be presented to the Panel again at a later meeting after those revisions have been made.

FORMAT AND SOPS

The Panel previously (September 2022) reviewed a compilation of all current and previous boilerplate/guidance documents used as standard operating procedures (SOPs). The changes suggested at that time were addressed and presented to the Panel at this meeting.