Post Meeting Announcement

Expert Panel for Cosmetic Ingredient Safety
165th Meeting (June 12 - 13, 2023) - Findings

June 15, 2023

● Final Safety Assessments

- **5-Amino-6-Chloro-*o*-Cresol – 1 ingredient – Safe for use as a hair dye**
- **Hyaluronates – 7 ingredients – Safe**
- **Phytosteryl Glutamates – 3 ingredients – Safe**

● Tentative Safety Assessments

- **6-Amino-*m*-Cresol – 1 ingredient – Insufficient data**
- **6-Amino-*o*-Cresol – 1 ingredient - Insufficient data**
- **Olive – 23 ingredients – Split conclusion (16 safe; 7 insufficient)**
- **Phenyl-Substituted Methicones – 7 ingredients – Mixed (safe/insufficient)**
- **Polyglycerins – 4 ingredients - Safe**
- ***Zanthoxylum piperitum* – 4 ingredients – Safe with qualifications**

● Insufficient Data Announcement

- **MIBK – 1 ingredient**
- **Prostaglandins Analogues – 2 ingredients**
- **Yeast ingredients – 56 ingredients**

● Tabled

- **Fatty Amphocarboxylates – 11 ingredients**

● 165th Meeting Notes

- **Director's Report**
- **Re-Reviews – 3 re-opened; 2 conclusions reaffirmed**
- **Re-Review summaries – 3 approved**
- **2024 Priorities Request**
- **Nitrosation Resource Document**
- **Format and SOPs**
- **Scientific Literature Reviews – available or under development**
- **Next Expert Panel Meeting – Monday and Tuesday, September 11-12, 2023**

Final Safety Assessments

Final safety assessments will be posted on the Cosmetic Ingredient Review (CIR) website at www.cir-safety.org. Unpublished data cited as references in CIR safety assessments are available for review. Any interested person who has sound scientific evidence that a final safety assessment is incorrect may petition the Expert Panel for Cosmetic Ingredient Safety (Panel) to amend the safety assessment.

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

For the tentative safety assessments listed below, to be posted on the CIR website (www.cir-safety.org) in the near future, interested persons are given 60 days from the posting date to comment, provide information, and/or request an oral hearing before the Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings and are available for review by any interested party. Please submit data and/or comments to CIR ***as soon as possible, but no later than 60 days from the actual posting date of the report, for full consideration. Submissions received thereafter may be in jeopardy of not being considered by the Panel.*** *The updated reports may be scheduled for review by the Panel as early as at the* ***September 11-12, 2023*** *meeting.*

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*
Hydrolyzed Olive Fruit Extract*
Hydrolyzed Olive Leaf Extract*
Olea Europaea (Olive) Fruit
Olea Europaea (Olive) Fruit Extract
Olea Europaea (Olive) Fruit Juice*
Olea Europaea (Olive) Fruit Juice Extract*
Olea Europaea (Olive) Fruit Unsaponifiables
Olea Europaea (Olive) Fruit Water*
Olea Europaea (Olive) Husk Powder*
Olea Europaea (Olive) Leaf*
Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Seed*
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) Branch Extract**
Olea Europaea (Olive) Bud Extract
Olea Europaea (Olive) Flower Extract**
Olea Europaea (Olive) Flower Water**
Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Wood 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
Diphenylsiloxy Phenyl Trimethicone
Diphenylsiloxy Phenyl/Propyl Trimethicone
Phenyl Dimethicone
Phenyl Methicone
Phenyl Trimethicone
Trimethylsiloxyphenyl 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

For these insufficient data announcements, interested persons are given an opportunity to comment, provide information and/or request an oral hearing before the Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings and are available for review by any interested party. Please submit data and/or comments to CIR ***as soon as possible, but no later than August 14, 2023, for full consideration****.* ***Submissions received thereafter might not be considered by the Panel at their next meeting.*** *These reports may be scheduled for review by the Panel as soon as the* ***September 11-12, 2023 meeting****.*

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

165th Meeting Notes

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; CTFA), the FDA, and the Consumer Federation of America (CFA) 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 (SSC), and all other participants.

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.

Scientific Literature Reviews

The following Scientific Literature Reviews (SLRs) are either posted at the CIR website, or, are currently under development and may be posted imminently. These may then be presented to the Panel for their review (as Draft Reports) during the next few meetings.

.

Charcoal Powder
Copper Gluconate
HC Blue No. 15
1,2,4-Trihydroxybenzene
Inositol
Lactobacillus Ferment ingredients
Palmitoyl Pentapeptide-4 group
Paeonia suffruticosa-derived ingredients
Pelargonium graveolens-derived ingredients
Pyridoxine and Pyridoxine HCl

Next Expert Panel Meeting

Monday and Tuesday, September 11-12, 2023, to be held ***in-person*** at the Melrose Hotel, 2430 Pennsylvania Avenue, NW, Washington, DC.

Please check the CIR website for details as the meeting approaches. The link will be available approximately a month before the meeting and will be found on the 166th meeting page of the CIR website. https://www.cir-safety.org/