Post Meeting Announcement

Expert Panel for Cosmetic Ingredient Safety
166th Meeting (September 11 - 12, 2023) - Findings

September 15, 2023

- **Final Safety Assessments**
  - **6-Amino-*m*-Cresol – 1 ingredient – Insufficient Data**
  - **6-Amino-*o*-Cresol – 1 ingredient – Insufficient Data–No Reported Use**
  - ***Olea europaea* (Olive)-Derived Ingredients – 23 ingredients – Split conclusion (16 safe; 7 insufficient)**
  - **Polyglycerins – 4 ingredients – Safe**
  - **Phenyl-Substituted Methicones – 7 ingredients – Safe (excluding products which may be incidentally inhaled)**
  - ***Zanthoxylum piperitum*–Derived Ingredients – 4 ingredients – Safe (when formulated to be non-sensitizing)**

- **Tentative Safety Assessments**
  - **5-Amino-4-Chloro-o-Cresol & HCl salt – 2 ingredients – Insufficient Data (for risk assessment)**
  - **Charcoal Ingredients – 4 ingredients - Safe**

- **Insufficient Data Announcement**
  - **Pentapeptide Ingredients – 3 ingredients**

- **166th Meeting Notes**
  - **Director's Report**
  - **Re-Reviews – 2 re-opened; 4 conclusions reaffirmed**
  - **Re-Review summaries – 2 approved**
  - **2024 Final Priorities**
  - **Nitrosation Resource Document**
  - **Toluene Strategy**
  - **Dermal Dose and Presentation**
  - **Hair Dye Epidemiology**
  - **FDA and SCCS Guidance**
  - **Scientific Literature Reviews – available or under development**
  - **Next Expert Panel Meeting – Monday and Tuesday, December 4-5, 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 Unpublished data cited as references in CIR safety assessments are available for review.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.

6-Amino-*m*-Cresol

The Panel issued a Final Amended Report with the conclusion that the available data are insufficient to make a determination that 6-Amino-*m*-Cresol is safe under the intended conditions of use as a hair dye ingredient. 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

The Panel determined that these data needs, from the original Insufficient Data Announcement (IDA) issued following the December 2022 Panel meeting, remain unmet. If these needs remain unmet after 2 years (September 15, 2025), this insufficient data conclusion will be transmuted to "Use Not Supported."

6-Amino-*o*-Cresol

The Panel issued a Final Amended Report with the conclusion that the available data are insufficient to make a determination that 6-Amino-*o*-Cresol is safe under the intended conditions of use as a hair dye ingredient. 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

The Panel determined that these data needs, from the original IDA issued following the December 2022 Panel meeting, remain unmet. Since there are currently no reported uses of this ingredient, this insufficient data conclusion is immediately transmuted to "Insufficient Data–No Reported Use."

***Olea europaea* (Olive)-Derived Ingredients**

The Panel issued a Final Report 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 that the following 7 *Olea europaea* (olive)-derived ingredients are safe 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. Accordingly, the conclusion for these ingredients is immediately transmuted to "Insufficient Data–No Reported Use."*

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 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

Polyglycerins

The Panel issued a Final Report with the conclusion that the following 4 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Diglycerin	Polyglycerin-6
Polyglycerin-3	Polyglycerin-10

The Panel considered their prior safety determination of glycerin that was issued in 2019 and found it reasonable to use this information as supporting data for repeated dose oral toxicity, developmental and reproductive toxicity, and carcinogenicity endpoints. Additionally, the Panel discussed the otherwise robust toxicological profile, including negative dermal irritation and sensitization data, and that the negative log K_{ow} values for these ingredients (ranging from -8.6 to -2) would preclude absorption in the skin.

Linear Phenyl-Substituted Methicones

The Panel issued a Final Report for these 7 linear phenyl-substituted methicone ingredients and 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 a memorandum sent by the Silicones, Environmental, Health, and Safety Center (SEHSC) confirming that data submitted on Phenyl Trimethicone was actually on the material associated with CAS No. 70131-69-0 (i.e., polyphenylsilsesquioxane). Thus, the Panel agreed that these data are not appropriate for inclusion in the report. The Panel also discussed that because CAS No. 70131-69-0 initially had been erroneously associated with Phenyl Trimethicone, the reported frequencies and concentrations of use for Phenyl Trimethicone may be inflated.

The Panel agreed that data on short-term intermittent-exposure inhalation toxicity and on the particle size distribution and concentrations of use for these ingredients in products which may be incidentally inhaled are lacking. Thus, the Panel deemed the available data insufficient to make a determination of safety for these ingredients in products which could be incidentally inhaled.

***Zanthoxylum piperitum*–Derived Ingredients**

The Panel issued a Final Report 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 although there was a lack of general toxicity data, *Zanthoxylum piperitum* extract is classified as generally recognized as safe (GRAS) in foods, and its GRAS status mitigated toxicity concerns. Additionally, *Zanthoxylum piperitum*-derived ingredients have low reported maximum concentrations of use (i.e., 0.01%).

For *Zanthoxylum piperitum*-derived ingredients, the Panel was concerned about the presence of multiple terpene constituents (e.g., citronellol and geranyl acetate) in cosmetic ingredients, which could result in sensitization reactions. A human repeated-insult patch test (HRIPT) of a *Zanthoxylum piperitum* extract in ethanol at 2% deemed the test substance neither a sensitizer nor an irritant. However, 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. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

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* ***December 4-5, 2023*** *meeting.*

5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl

The Panel issued a Tentative Amended Report with the conclusion that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for these hair dye ingredients, the Panel will be conducting a margin of safety calculation based on the available data in this safety assessment. Once this calculation is performed and reviewed by the Panel at the next meeting, a final determination of safety will likely be made. No further data is requested at this time.

Plant-Derived Charcoal Ingredients

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

Charcoal	Charcoal Powder
Charcoal Extract	Activated Charcoal *

**Not in the web-based International Cosmetic Ingredient Dictionary and Handbook (wINCI; Dictionary)*

Both the *Dictionary* and communications with the International Nomenclature Committee (INC) indicate that the source material for these cosmetic ingredients is plant-based, while carbon black (not an ingredient in this report) is sourced from minerals (e.g., petroleum). Clarification on the ingredient source for Activated Charcoal is being sought; however, the data in the report indicate it is also sourced from plants (e.g., bamboo). Carbon black and ingredients derived from mineral sources are not produced in the same manner (e.g., sourced from petroleum instead of plants) and are likely to have different compositions and impurities. The data in the report are specific to the plant-based materials and do not include carbon black.

The Panel discussed the issue of incidental inhalation exposure that may occur from the use of these ingredients in cosmetic formulations (i.e., Charcoal Powder is used in a hair spray at 0.001%). Limited data available from inhalation studies, including an acute rat study with Charcoal and an intratracheal rat carcinogenicity study with Charcoal Powder, suggest little potential for respiratory effects at relevant doses. The Panel considered other data available to characterize the potential for plant-derived Charcoal ingredients to cause systemic toxicity, irritation, sensitization, and genotoxicity. They noted the lack of systemic toxicity in acute and repeated dose studies at up to 11,240 mg/kg bw, a lack of irritation and sensitization in tests of dermal exposure, and the absence of genotoxicity in *in vitro* and *in vivo* test systems. Thus, based on all these findings, the Panel determined that plant-derived Charcoal ingredients are safe as used in cosmetics in the present practices of use and concentration described in the safety assessment.

Insufficient Data Announcement

For this insufficient data announcement, 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 November 6, 2023, for full consideration****.* ***Submissions received thereafter might not be considered by the Panel at their next meeting.*** *This report may be scheduled for review by the Panel as soon as the* ***December 4-5, 2023 meeting****.*

Pentapeptides

The Panel issued an insufficient data announcement for Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4. The additional data needed to determine the safety of these ingredients are:

- Dermal irritation and sensitization data for the lysine-threonine-serine-lysine-serine (KTSKS) amino acid sequence
- Skin penetration and degradation data for Myristoyl Pentapeptide-4 (KTSKS sequence)
- Clarification of the concentration of use tested in the HRIPT study currently summarized in the report on Palmitoyl Pentapeptide-4 (Pal-lysine-threonine-threonine-lysine-serine; Pal-KTTKS) sequence

166th Meeting Notes

Director's Report

Dr. Heldreth thanked the members of and liaisons to the Expert Panel for Cosmetic Ingredient Safety, and noted that in addition to the 9 reports advancing in the review process, there was much discussion regarding numerous administrative items, with a collective eye to modernizing CIR and support for this Panel. The CIR Staff plans to investigate further modernization, including new methodologies, tools, and various notes of guidance to better support this Panel. Dr. Heldreth also thanked Dr. Bjerke for the timely and extremely relevant presentation, "Skin Sensitization Risk Assessment and Confidence in New Approach Methodologies" (linked below).

In addition to presenting the great work of this Panel in June 2023 at the DGK/IKW: "Safety is the Key" - Scientific Conference on Safety Assessment (https://sicherheitsbewerter.info/veranstaltungsberichte/), Dr. Heldreth noted a reoccurring theme at the conference regarding these new methodologies and the importance of risk assessment in building confidence therein.

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 6 previous assessments for re-review. The Panel determined that the following 2 reports should be reopened; a Draft Amended Report will be presented to the Panel for each of these safety assessments at a later meeting.

- *Acacia senegal*-Derived Ingredients – 2 ingredients
- *t*-Butyl Alcohol – 1 ingredient

In contrast, the Panel reaffirmed the conclusions reached for the following 4 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.

- Isobutane, Isopentane, Butane, and Propane – 4 ingredients
- Laneth-9 Acetate and Laneth-10 Acetate – 2 ingredients
- Sodium Dehydroacetate and Dehydroacetic Acid – 2 ingredients
- Zinc Phenolsulfonate – 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 2 re-review summaries:

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

2024 Final Priorities

There are 18 reports planned, covering 31 ingredients, on the 2024 Final Priorities List. While the priority list below includes only the lead ingredients, groupings of ingredients can be found on the CIR website. Reports previously prioritized and on the CIR docket at the end of 2023, as well as an extensive number of re-reviews of previous assessments, will supplement the total number of reports/ingredients to be assessed in 2024. Interested parties are encouraged to submit pertinent data to the CIR, as soon as possible, for use in the development of the Scientific Literature Reviews (SLR) for these ingredients. Although the specific data needs vary for each safety assessment, the following are typical data that the Panel reviews for each safety assessment.

- Chemistry, impurities, and method of manufacture
- Risk (e.g., margins of safety)
- Toxicokinetics data, specifically dermal absorption and/or penetration
- Repeated-dose toxicity data
- Inhalation toxicity data, if the ingredient is used in a product that can be incidentally inhaled
- Reproductive/developmental toxicity data
- Genotoxicity data; if positive, carcinogenicity data may be needed
- Dermal irritation and sensitization data at maximum concentration of use

For the review of botanical ingredients (natural complex substances (NCS)), the additional data needed include: species, plant part, extraction method, solvent, and data on component chemical characterization. It is important that these data are specific for the ingredient(s) as used in cosmetics.

2024 Final Priorities List

Ingredient	Frequency of Use (FOU) Data Year: 2023
For cause	
Cannabidiol	32
Basic Blue 7	1
Trimethylbenzoyl Diphenylphosphine Oxide	127
Tetrabromophenol Blue	2
Per FOU	
Polyacrylate-13	**265**
Polygonum Cuspidatum Root Extract	**245**
Xylitylglucoside	**213**
Phytosphingosine	**210**
Sodium Hyaluronate Crosspolymer	**207**
Polyacrylate Crosspolymer-6	**205**
Trimethylpentanediyl Dibenzoate	**202**
Tosylamide/Epoxy Resin	**189**
Carnosine	**184**
Madecassoside	**182**
Sophora Flavescens Root Extract	**179**
Curcuma Longa (Turmeric) Root Extract	**177**
Lonicera Japonica (Japanese Honeysuckle) Flower Extract	**175**
Perfluorohexylethyl Triethoxysilane	**172**

Nitrosation Resource Document

The Panel discussed the FDA's guidance for industry regarding the recommended acceptable intake limits for nitrosamine drug substance-related impurities (NDSRIs). The Panel deliberated on the potential utilization of the approach, as proposed in the guidance document, to predict and categorize the carcinogenic potency of nitrosamine impurities in evaluating the safety of cosmetic products. The Panel noted the distinctions in usage scenarios between cosmetics and orally administered drugs should be considered, with special discussion on elements such as formulation, levels of exposure, rates of absorption, and so forth. The Panel concurred that the guidance document should be cited in CIR's nitrosation resource document, which is currently being prepared, integrating pertinent and valuable information.

Toluene Strategy

A Final Report on Toluene was first published in 1987, with a conclusion of safe in the present practices of use and concentration, as described in that report. This conclusion was re-affirmed in a re-review published in 2006. In March 2023, Toluene was nominated for the 2024 Priority List by the FDA, and in June 2023, the Panel agreed to accelerate the re-review of this ingredient. Following this request, a literature search was performed on Toluene for studies dated 1983 forward, and a vast number of studies were found on many toxicological endpoints and effects related to human health. Due to the volume of literature found, at the September 2023 meeting, CIR staff presented a strategy memo to the Panel requesting guidance on what information should be included in the future Draft Amended Report. The Panel agreed to include studies published after 2005, excluding studies associated with high exposures and studies assessing repetitive occupational exposures. In addition to the Draft Amended Report, abstracts and citations of the studies not included in that report will be presented to the Panel for assessment for potential inclusion. In addition, the Panel noted that all governmental regulatory guidelines (e.g., National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit of 100 ppm (10 h time-weighted exposure); 150 ppm (short term exposure limit)) should be included in the report, along with a

margin of safety calculation, similar to the calculation performed by the Danish Environmental Protection Agency (EPA) on formaldehyde. (For a more cautious exposure estimate, calculation should account for exposure to 20 nails, instead of 10 as used by the Danish EPA.)

Dermal Dose and Presentation

The Panel deliberated on the dose metrics used in the HRIPT. The Panel noted dose per unit area of skin is one of the important factors in interpretation of existing HRIPT data, which can be further employed to derive a No Expected Sensitization Induction Level (NESIL) using the QRA2 (Skin Sensitization Quantitative Risk Assessment 2) approach, in consideration of accumulative exposure of diverse cosmetic products that might be used consistently over prolonged durations. To ensure safety, the Panel intends to evaluate the concentration of the test substance in an HRIPT, expressed as dose per skin unit area; additionally, on a case-by-case basis, the Panel will consider other factors that further affect the sensitivity and reliability of the test, such as contact area, skin site permeability, and occlusion, etc.

Dr. Don Bjerke, Chair of the CIR Science and Support Committee, delivered a wonderfully informative presentation titled "Skin Sensitization Risk Assessment and Confidence in New Approach Methodologies." The presentation provided interpretation of HRIPT data, emphasizing the importance of using dose per skin unit area as an appropriate dose metric for skin sensitization risk assessment, and further showcased the evolution and utilization of new approach methodologies (NAMs) for accessing skin sensitization risks. The presentation is available on the meeting page,

https://www.cir-safety.org/sites/default/files/166th%20CIR%20NAM%20Update%20Don%20Bjerke.pdf.

Hair Dye Epidemiology

The Panel reviewed the revised draft of the Hair Dye Epidemiology Resource Document. The Panel restated its commitment to continuous surveillance of the latest epidemiological data concerning the association between personal hair dye use and human cancer risk. The Panel discussed the significance of the Hair Dye Epidemiology Resource Document as a living document for incorporating the forthcoming epidemiological data. The Panel determined the conclusion of the document would be periodically reassessed, in light of new information. Additionally, the Panel deliberated on broadening the document's influence by making it more accessible to the public. This document will be brought before the Panel again prior to finalization.

FDA and SCCS Guidance

The Panel looked at 2 guidance documents, the *Draft Guidance for FDA Registration and Listing of Cosmetic Product Facilities and Products* (FDA Registration; FDA-2023-D-1716) and the *SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation - 12th revision* (SCCS NoG; SCCS/1647/22). The US FDA published their FDA Registration document to, in part, provide an opportunity for input on the creation of a new, mandatory cosmetic ingredient registration program. The Panel lauded this endeavor and looks forward to utilizing the resulting frequency of use data generated therein.

The Panel also thoroughly evaluated the SCCS NoG document and provided CIR Staff with significant input on the creation of a similar "CIR Notes of Guidance." This venture will assist CIR in their efforts to modernize.

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.

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

Next Expert Panel Meeting

Monday and Tuesday, December 4-5, 2023, to be held ***virtually*** via Microsoft Teams. 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 167th meeting page of the CIR website. https://www.cir-safety.org/