Cosmetic Ingredient Review

Post Meeting Announcement

Expert Panel for Cosmetic Ingredient Safety
171st Meeting (December 2 – 3) - Findings

December 6, 2024

● Final Safety Assessment

- **Inositol – 1 ingredient – Safe as used**

● Tentative Safety Assessments

- ***p*-Phenylenediamine– 3 ingredients – Split conclusion (safe as hair dyes; unsafe as dermal, eyebrow, or eyelash dyes)**
- **4-Chloro-2-Aminophenol – 1 ingredient – Insufficient data conclusion**
- **Tetrabromophenol Blue – 1 ingredient – Safe as a hair dye**
- ***Paeonia suffruticosa* - 5 ingredients – Split conclusion (safe as used for 1 ingredient; insufficient data for 4 ingredients)**

● Insufficient Data Announcements

- **Pyrogallol – 1 ingredient**
- **Cocoyl Hydrolyzed Collagens – 4 ingredients**
- ***Nelumbo nucifera* – 14 ingredients**

● 171st Meeting Notes

- **Director's Report**
- **Re-Reviews**
  - **2 reopened (Nitrophenylenediamines & Oxyquinoline)**
  - **2 reaffirmed summaries approved (Castor Oil & PEG Stearates)**
- **Inhalation Resource Document**
- **MOE Resource Document**
- **Strategy Memo – Fatty Amphocarboxylates**
- **Scientific Literature Reviews – available or under development**
- **Next Expert Panel Meeting – Thursday and Friday, March 13 - 14, 2025 – *In-person***
  - ***All submissions for this meeting should be received by CIR no later than January 27, 2025***

Final Safety Assessment

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 Unpublished data cited as references in CIR safety assessments are available for review.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.

Inositol

The Panel reviewed the available data and issued a Final Report with the conclusion that Inositol is safe in cosmetics in the present practices of use and concentration as described in the safety assessment. According to 2023 FDA VCRP survey and 2022 concentration of use data, this ingredient is used in 212 formulations and at up to 2%. However, according to concentration of use data updated in 2024, Inositol is used at up to 4% in face and neck preparations. The Panel noted this increased concentration of use, and determined that the available data are still in support of the safe use of this ingredient. The safety of Inositol is supported by its widespread use, GRAS status, endogenous nature, low concentrations of use, and lack of positive alerts in various toxicological studies.

Tentative Safety Assessments

For the tentative safety assessments listed below, to be posted on the CIR website (https://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 at the next review.*** *The updated reports may be scheduled for review by the Panel as early as at the* ***March 13 - 14, 2025 meeting.***

p-Phenylenediamine, *p*-Phenylenediamine HCl, and *p*-Phenylenediamine Sulfate

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

p-Phenylenediamine *p*-Phenylenediamine HCl *p*-Phenylenediamine Sulfate

However, the Panel also concluded that these ingredients are unsafe for use in dermal coloring applications (e.g., temporary black henna tattoos) and for use in eyelash and eyebrow dyes.

p-Phenylenediamine is a known dermal sensitizer. It is highly inappropriate for this ingredient to be used in products outside of hair dyes as evidenced by multiple case reports of severe adverse skin reactions to dark henna temporary tattoos. Reactions include severe allergic contact dermatitis, permanent hyper-and hypopigmentation, and keloid formation. *p*-Phenylenediamine is an unapproved color additive in cosmetic products, and thereby, such use is not permitted under the US Federal Food, Drug and Cosmetic Act (FD&C Act), which mandates that color additives must be approved by the FDA for their intended use before they are used. *p*-Phenylenediamine is exempt from certain adulteration and color additive provisions of the FD&C Act only when it is used as a coal tar hair dye.

In addition, the Panel noted that use of *p*-Phenylenediamine has been reported in eye makeup preparations, non-coloring hair preparations, and skin care preparations. Accordingly, because *p*-Phenylenediamine is not an approved color additive in cosmetics products, use in eye makeup products, non-coloring hair preparations, and skin care preparations is not permitted. Furthermore, the Panel noted that hair dyes, such as those containing *p*-Phenylenediamine, should not be applied to the eyebrows and eyelashes in that such use can result in lost or permanently damaged vision.

4-Chloro-2-Aminophenol

The Panel issued a Tentative Amended Report for public comment with the conclusion that the available data are insufficient to make a determination that 4-Chloro-2-Aminophenol is safe under the intended conditions of use in hair dye formulations. The Panel determined that the data needs from the Insufficient Data Announcement (IDA) issued following the June 2024 Panel meeting remain unmet. In order to come to a conclusion of safety for this hair dye, the following data are needed:

- Maximum concentration of use data
- Composition/impurities data
- Toxicokinetics data, especially dermal absorption data
    - If absorbed, additional data, including developmental and reproductive toxicity data, may be needed
- Micronucleus genotoxicity assay data

Tetrabromophenol Blue

The Panel issued a Tentative Report for public comment with the conclusion that Tetrabromophenol Blue is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment.

Tetrabromophenol Blue is reported to function as a hair colorant and is used in oxidative and direct hair dye products. The Panel recognizes that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal 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.

Paeonia suffruticosa – Derived Ingredients

The Panel issued a Tentative Report for public comment with a conclusion of safe in cosmetics in the present practices of use and concentration as described in the safety assessment for Paeonia Suffruticosa Seed Oil. The safety of this ingredient is supported by its chemical composition and very low concentration of use. However, the Panel also issued an insufficient data conclusion regarding the 4 remaining *Paeonia suffruticosa*-derived ingredients.

Paeonia Suffruticosa Bark Extract	Paeonia Suffruticosa (Tree Peony) Root Bark Extract
Paeonia Suffruticosa Extract	Paeonia Suffruticosa Root Extract

For these 4 ingredients, the Panel determined that data needs from the IDA issued following the June 2024 Panel meeting remain unmet. In order to come to a conclusion of safety for these ingredients, the following data are needed:

- For Paeonia Suffruticosa Root Bark Extract
  - Clarification on the definition, method of manufacture, and composition, as applicable to cosmetic use
  - Clarification as to whether Paeonia Suffruticosa Root Extract included the root bark of the plant
- For Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, and Paeonia Suffruticosa Root Extract
  - Maximum concentrations of use
  - Ocular irritation data (in vitro) at the maximum reported concentrations of use for uses near the eye
- For all 4 insufficient ingredients:
  - 28-Day dermal toxicity assays on all ingredients
    - if positive, data on systemic toxicity endpoints (e.g., developmental and reproductive toxicity) may be needed
  - Genotoxicity data
- For Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, and Paeonia Suffruticosa (Tree Peony) Root Bark Extract:
  - Dermal irritation and sensitization data

Insufficient Data Announcements

For these insufficient data announcements (IDAs), 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 February 4, 2025, 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* ***March 13 - 14, 2025 meeting****.*

Pyrogallol

The Panel issued an IDA for Pyrogallol. The following information is required to determine the safety of this hair dye:

- Maximum concentration of use
- Dermal irritation and sensitization data at maximum concentration of use for non-hair dye uses
- Ocular irritation data at maximum concentration of use for products used around the eyes

Cocoyl Hydrolyzed Collagens

The Panel issued an IDA for Potassium Cocoyl Hydrolyzed Collagen and TEA-Cocoyl Hydrolyzed Collagen. The additional data needed to determine the safety of these ingredient are:

- Maximum concentration of use
- Dermal irritation and sensitization data at a maximum concentration of use that does not induce sensitization
- UV absorption spectra; if absorbed, phototoxicity and/or photosensitization data are needed

In addition to Potassium Cocoyl Hydrolyzed Collagen and TEA-Cocoyl Hydrolyzed Collagen, the Panel has considered the addition of Cocoyl Hydrolyzed Collagen and Sodium Cocoyl Hydrolyzed Collagen. While CIR will conduct a full search of the publicly available literature for these 2 additional ingredients, all relevant unpublished data, including the data needs above, are requested for these ingredients.

Nelumbo nucifera – Derived Ingredients

The Panel issued an IDA after reviewing the safety information related to 14 *Nelumbo nucifera*-derived ingredients. The additional data needed to determine the safety of these ingredients are:

- For all ingredients
  - Composition and impurities
  - Method of manufacturing
  - 28-Day dermal toxicity assays on all ingredients
    - if positive, additional data (e.g., developmental and reproductive toxicity data) may be needed
  - In vivo genotoxicity data
  - UV absorption spectra

- For the callus, phytoplacenta, and stamen derived ingredients
  - Dermal irritation and sensitization data at maximum concentration of use
- For all except the flower and germ derived ingredients
  - In vitro genotoxicity data
- For the flower and whole plant derived ingredients
  - Developmental and reproductive toxicity data
- For all except the flower derived ingredients
  - In vitro ocular

171st Meeting Notes

Director's Report

Dr. Heldreth thanked the members of and liaisons to the Panel for their tireless efforts to protect consumers. He also thanked colleagues at the Office of Cosmetics and Colors (OCAC) for their assistance in understanding the US FDA Registration and Listing Data (RLD), which CIR received in response to a FOIA request this summer. While CIR had grown accustomed to the format of the VCRP data received in the past, colleagues at the OCAC have since been very helpful with adjusting to the differences in the format of the RLD. In additional news from OCAC, Dr. Linda Katz announced her upcoming retirement from the FDA. Dr. Katz has been the Director of the Office for over 20 years, as well as the FDA liaison to this Panel for the same course of years. CIR and the Panel recognized and thanked Dr. Katz for her monumental contributions to public safety over the last few decades.

Dr. Katz

Dr. Slaga

Additionally, Dr. Heldreth announced the retirement of Dr. Tom Slaga. Dr. Slaga, a noted cancer expert, Panel member, and friend, formally retired from this Panel. He is an absolute giant in the field of cancer research, leaving some large shoes to fill. Dr. Slaga served this Panel for many years, and we will dearly miss working with him. Largely due in part to his retirement, the CIR Steering Committee convened in November of this year. The Committee was spoiled for choice with 6 excellent candidates to be elected to just one position on the Panel. After much deliberation, the Committee elected Dr. Sam Cohen, MD, PhD, Havlik-Wall Professor of Oncology in the University of Nebraska Medical Center, Department of Pathology and Microbiology to this Panel. His tenure with the Panel will commence with the March 2025 meeting.

Dr. Sam Cohen

The Committee also approved the addition of 2 new rereview report pathways for the Panel's use. When the Panel is presented with a rereview proposal wherein the use of an ingredient has been discontinued, they may proceed to immediately issue a "use not supported" conclusion. As well, when the Panel is presented with a rereview proposal wherein no change of conclusion is desired but expanded summarization and publication of the new data therein would be in the best interest of the public, they may immediately issue an "expanded rereview summary" inclusive of expanded data recitations.

Also of note in 2024, Dr. Heldreth highlighted the issuance of 4 CIR issues of the *International Journal of Toxicology* (IJT). All 4 of CIR's 2024 IJT issues are now published, directly accessible in standard format at IJT (https://journals.sagepub.com/loi/IJT), and free, report-by-report, from both the CIR portal (https://cir-reports.cir-safety.org/) and PubChem (https://pubchem.ncbi.nlm.nih.gov/source/Cosmetic%20Ingredient%20Review%20(CIR)). Additionally, copies of these issues in IJT's Nxtbook format, are available here:

Feb 2024- https://www.nxtbook.com/sage/sage/ijt_cir_202402/

Apr 2024- https://www.nxtbook.com/sage/sage/ijt_cir_202404/

Aug 2024- https://www.nxtbook.com/sage/sage/ijt_cir_202408/

Oct 2024- https://www.nxtbook.com/sage/sage/ijt_cir_202410/

Furthermore, CIR is extremely delighted about the establishment this year of a cooperation agreement with the International Collaboration of Cosmetics Safety and presentations on cosmetic ingredient risk & safety assessment in both China and South Korea, by CIR Toxicologist Dr. Jinqiu Zhu.

Rereviews

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 2 previous assessments for rereview. The Panel determined that the following reports should be reopened; Draft Amended Reports will be presented to the Panel for these rereviews at a future meeting.

- 2-Nitro-*p*-Phenylenediamine & 4-Nitro-*o*-Phenylenediamine – 2 ingredients
- Oxyquinoline & Oxyquinoline Sulfate – 2 ingredients

The Panel reaffirmed the conclusions reached in these 2 safety assessments (i.e., chose not to re-open the original reports) at a prior meeting. A rereview summary for each of these safety assessments was prepared and presented to the Panel at this meeting. The Panel approved both of these documents.

- Castor Oil - 8 ingredients
- PEG Stearates – 30 ingredients

Inhalation Resource Document

The Panel reviewed the revised Inhalation Resource Document and the respiratory boilerplate (BP) language therein. The Panel discussed the suitability of applying the BP to address various categories of cosmetic spray products, with particular focus on the precise characterization of respiratory fractions of particles/droplets generated during uses of different spray products. Additionally, the Panel considered some special aspects of cosmetic spray safety evaluation, including the assessment of nanoparticle exposure in non-airbrush spray products, the limitations of applying the Occupational Safety and Health Administration (OSHA) permissible exposure limits (PEL), the regional lung deposition of aerosols and particles and the associated toxic effects in both the upper and deep respiratory tract, as well as the feasibility of obtaining the necessary data through RLD for assessing the safety of ingredients used in airbrush devices. After the suggested changes and relevant concerns are addressed, the document and the BP will be presented to the Panel for further review at a future meeting.

MOE Resource Document

The Panel reviewed a draft margin of exposure (MOE) resource document and discussed the varying terminology used in the systemic quantitative risk assessment (QRA). They further deliberated the application of using known values, rather than parameters that are conservative. The Panel requested revisions to the document to address the received comments, clarify the preferred terminology, and differently apply uncertainty factors to improve the estimation of systemic exposure doses. Upon addressing these concerns, the document will be resubmitted to the Panel for further review at a future meeting.

Strategy Memo – Fatty Amphocarboxylates

The Panel responded to a strategy memo regarding received data (quantitative structure-activity relationship (QSAR) skin sensitization predictions on C12 diacetate 1, C12 diacetate 2, C12 monoacetate 1, and C12 monoacetate 2) and a statement from the Amphoacetates Consortium suggesting the tabling of this report for forthcoming DART data. Following deliberations with industry, the Panel are expecting additional data on the chemical structures, composition, and impurities on these ingredients to aid with the review of this group, and to determine whether the use of this read-across approach is appropriate. In addition, the Panel agreed to table the Fatty Amphocarboxylates report to allow for the receipt of a prenatal developmental toxicity study in rabbits performed using C8-18 (diacetate form). All data are requested to be submitted as soon as possible. The next iteration of this report will be presented to the Panel at either their June or September meetings in 2025, depending in part on the timing of relevant data submissions.

Scientific Literature Reviews

The following Scientific Literature Reviews (SLRs) are either posted on 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.

Cannabidiol
Centaurea cyanus flower-derived ingredients
Dimer Dilinoleate group
HC Blue No. 15
Houttuynia cordata-derived ingredients
Lactobacillus ferment ingredients
Pelargonium graveolens-derived ingredients
Pyridoxine and Pyridoxine HCl
Sigesbeckia Orientalis Extract
Sodium Hydrosulfite
Salix alba (Willow)-derived ingredients
Trimethylbenzoyl Diphenylphosphine Oxide

Next Expert Panel Meeting

Thursday and Friday, March 13 - 14, 2025, to be held ***in-person***, at the Marriott Georgetown, 1221 22nd Street NW, Washington, DC 20037. Please check the CIR website for details as the meeting approaches. https://www.cir-safety.org/

Expert Panel for Cosmetic Ingredient Safety 2025 Meetings Calendar

Date– In Person:	March 13th – 14th, 2025 (Thursday & Friday)
Location:	**Marriott Georgetown** 1221 22nd Street NW Washington, DC 20037
Date- In Person:	June 9th – 10th, 2025 (Monday & Tuesday)
Location:	**The Westin Georgetown** 2350 M Street NW Washington, DC 20037
Date:	September 8th –9th, 2025 (Monday & Tuesday)
Location:	Virtual
Date:	December 4th – 5th 2025 (Thursday & Friday)
Location:	Virtual