Cosmetic Ingredient Review

Post Meeting Announcement

Expert Panel for Cosmetic Ingredient Safety
172nd Meeting (March 13 – 14) - Findings

March 19, 2025

- **Final Safety Assessment**
  - **2,4-Diaminophenoxyethanol – 2 ingredients – Safe as hair dyes**
  - ***p*-Phenylenediamine – 3 ingredients – Split conclusion (safe as hair dyes; unsafe for dermal, eyebrow, or eyelash dyes)**
  - **Copper Gluconate – 1 ingredient – Safe as used**

- **Tentative Safety Assessments**
  - **Basic Blue 7 – 1 ingredient – Insufficient data conclusion**
  - ***Nelumbo nucifera* – 14 ingredients – Insufficient data conclusion**
  - **Octoxynols – 25 ingredients – Safe when formulated to be non-irritating**
  - **Propylene Carbonate - 1 ingredient – Safe when formulated to be non-irritating**

- **Insufficient Data Announcements**
  - **Butoxyethanol – 1 ingredient**
  - **Kojic Acid – 1 ingredient**
  - **Trimethylbenzoyl Diphenylphosphine Oxide – 1 ingredient**
  - ***Acacia senegal* - 2 ingredients**

- **172nd Meeting Notes**
  - **Director's Report**
  - **Re-Reviews**
    - **1 reaffirmed (Waxes)**
    - **1 split: 2 ingredients reaffirmed, 5 ingredients concluded as use not supported (Glyceryl Monoesters)**
  - **Inhalation Resource Document**
  - **MOE Resource Document**
  - **2026 Draft Priorities**
  - **Scientific Literature Reviews – available or under development**
  - **Next Expert Panel Meeting – Monday and Tuesday, June 9 - 10, 2025 – *In-person***
    - ***All submissions for this meeting should be received by CIR no later than May 9, 2025***

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 Unpublished data cited as references in CIR safety assessments are available for review.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

2,4-Diaminophenoxyethanol

The Panel issued a Final Amended Report with the conclusion that 2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate are safe for use as hair dye ingredients in the present practices of use and concentration described in the safety assessment.

2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate are reported to function as oxidative hair dye ingredients in hair coloring products. The Panel recognizes that hair dyes containing these ingredients, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the US Federal Food, Drug, and Cosmetic Act (FD&C Act) when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel expects that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

The Panel noted that 2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate have been reported to be used in eye makeup preparations. The FD&C Act mandates that color additives must be pre-market approved by the FDA for their intended use. 2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate are not approved color additives in cosmetic products, and thereby, use in eye makeup products is not permitted. The Panel also noted that hair dyes, such as these ingredients, should not be applied to the eyebrows and eyelashes in that such use can result in lost or permanently damaged vision.

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

The Panel issued a Final Amended Report 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 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.

The high degree of cross-reactivity between *p*-Phenylenediamine and other structurally related aromatic amines, including *p*-toluenediamine and aminophenols, poses a significant challenge in allergen avoidance. Studies indicate that a substantial proportion of *p*-Phenylenediamine-sensitized individuals exhibit concomitant reactivity to these compounds, highlighting the complexity of managing allergic contact dermatitis in this context.

Copper Gluconate

The Panel issued a Final Report with the conclusion that Copper Gluconate is safe for use as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment. The Panel noted that while there is a paucity of genotoxicity data in this safety assessment, carcinogenicity data from dietary studies on Copper Gluconate are available. While pre-neoplastic lesions were observed in these studies, along with nephrotoxic effects in an oral gavage study, the concentrations at which these adverse effects were observed are much greater than those used in cosmetic formulations. The US FDA has designated Copper Gluconate as generally recognized as safe (GRAS) as a direct food ingredient. Additionally, Copper Gluconate is not a dermal irritant or dermal sensitizer in human repeated insult patch tests. The Panel considered these findings, coupled with the low concentration of use in cosmetic products and negative developmental and reproductive toxicity data, and determined that the data were sufficient to conclude on the safety of Copper Gluconate.

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* ***June 9 - 10, 2025 meeting.***

Basic Blue 7

The Panel issued a Tentative Report for public comment with the conclusion that the available data are insufficient to make a determination of safety for Basic Blue 7 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 information is required:

- Chemical properties data

- Method of manufacturing
- Composition/impurities data
- Concentration of use
- Dermal absorption data or 28-d dermal toxicity data
    - If absorbed, additional data, including developmental and reproductive toxicity data are needed
- Genotoxicity data

Nelumbo nucifera

The Panel issued a Tentative Report for public comment with the conclusion that the available data are insufficient to make a determination of safety for the following 14 *Nelumbo nucifera* ingredients:

Nelumbo Nucifera Callus Culture Extract
Nelumbo Nucifera Extract
Nelumbo Nucifera Flower Extract
Nelumbo Nucifera Flower/Leaf/Stem Juice
Nelumbo Nucifera Flower Oil
Nelumbo Nucifera Flower Water
Nelumbo Nucifera Germ Extract
Nelumbo Nucifera Leaf Extract
Nelumbo Nucifera Phytoplacenta Culture Extract
Nelumbo Nucifera Root Extract
Nelumbo Nucifera Root Water
Nelumbo Nucifera Seed Extract
Nelumbo Nucifera Seed Powder
Nelumbo Nucifera Stamen Extract

The Panel determined that the data needs from the Insufficient Data Announcement (IDA) issued following the December 2024 Panel meeting remain unmet. In order to come to a conclusion of safety for these ingredients, the following data are therefore needed:

- For all ingredients
    - Composition and impurities
    - Methods of manufacturing
    - 28-d dermal toxicity data
        - if positive, additional data may be needed (e.g., development and reproductive toxicity data).
    - Ultraviolet (UV) absorption data (as well as more detailed information about the previously submitted UV spectra)
        - if absorbed, phototoxicity/photosensitization data (additional protocol details are needed for the previously-submitted studies)
- For the callus, phytoplacenta, stamen, and seed-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 flower and whole plant-derived ingredients
    - Developmental and reproductive toxicity data
- For all except flower and leaf-derived ingredients
    - In vitro ocular irritation data

Octoxynols

The Panel issued a Tentative Amended Report for public comment with the conclusion that the following 25 octoxynols are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulating to be non-irritating.

Octoxynol-1
Octoxynol-3
Octoxynol-5
Octoxynol-6
Octoxynol-7
Octoxynol-8
Octoxynol-9
Octoxynol-10
Octoxynol-11
Octoxynol-12
Octoxynol-13
Octoxynol-16
Octoxynol-20
Octoxynol-25
Octoxynol-30
Octoxynol-33
Octoxynol-40
Octoxynol-70
Octoxynol-9 Carboxylic Acid
Octoxynol-20 Carboxylic Acid
Potassium Octoxynol-12 Phosphate
Sodium Octoxynol-2 Ethane Sulfonate
Sodium Octoxynol-2 Sulfate
Sodium Octoxynol-6 Sulfate
Sodium Octoxynol-9 Sulfate

The Panel noted that there is currently no evidence of use in categories/products of concern for this ingredient group (i.e., baby products, products used near the eyes, or vaginal products) according to 2024 RLD. In addition, the Panel suggested UV absorption (and other) data from the previously issued report on octoxynols be included in this current iteration. Lastly, the Panel discussed the low reliability of certain genotoxicity assays (e.g., unscheduled DNA synthesis); while these data are still provided in the report, they should not be relied upon to determine genotoxicity.

Propylene Carbonate

The Panel issued a Tentative Amended Report for public comment with the conclusion that Propylene Carbonate is safe in cosmetics in the present practices of use and concentration as described in the safety assessment when formulated to be non-irritating. In September 2024, an IDA was issued for lack of concentrations of use in baby products and UV absorption data. No concentrations of use in baby products were received; however, since the primary concern therein was potential irritation, the Panel's conclusion caveat to formulate products containing this ingredient to be non-irritating, mitigates this concern. UV absorption data were received and considered sufficient by the Panel to eliminate phototoxicity/photosensitization concerns.

According to 2023 FDA VCRP data, Propylene Carbonate is reported to be used in 882 total formulations. RLD collected in 2024 indicate that Propylene Carbonate is used in 13,340 total formulations. This ingredient is used at up to 17.9% in leave-on products (according to 2022 concentration of use survey conducted by Council).

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 May 18, 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* ***June 9 - 10, 2025 meeting****.*

Butoxyethanol

The Panel issued an IDA for Butoxyethanol. The additional data needed to determine the safety of this ingredient are:

- Maximum concentration of use in hair dye formulations
- Maximum concentration of use in non-hair dye formulations

Kojic Acid

The Panel issued an IDA for Kojic Acid. The additional data needed to determine the safety of this ingredient are:

- A margin of exposure (MOE) calculation for whole body exposure
- An explanation as to why the European Union restricted use of Kojic Acid to the face and hands only

Trimethylbenzoyl Diphenylphosphine Oxide

The Panel issued an IDA for Trimethylbenzoyl Diphenylphosphine Oxide. The additional data needed to determine the safety of this ingredient are:

- Concentrations of use in non-nail products
- Dermal irritation and sensitization data at maximum use concentration for the skin
- Ocular irritation data (preferably at concentrations for products resulting in eye exposure, once received)
- MOE
- Phototoxicity/photosensitization data

Acacia senegal

The Panel issued an IDA for these 2 *Acacia senegal*-derived ingredients. The additional data needed to determine the safety of Acacia Senegal Gum and Acacia Senegal Gum Extract are:

- For both ingredients
  - UV absorption
    - If absorbed, phototoxicity/photosensitization data are needed
  - Ocular irritation data
- For Acacia Senegal Gum Extract
  - Composition/impurities
  - Method of manufacture
  - Irritation and sensitization data

172nd 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 from the Office of Cosmetics and Colors (OCAC) for their ongoing assistance, even in the face of organizational upheavals. Additionally, he thanked Dr.

Don Bjerke, who announced his pending retirement, after years of dutiful service to the Panel as the Chair of the CIR Science and Support Committee.

This meeting was the first for new Panel member, Dr. Samuel M Cohen, MD, PhD, Havlik-Wall Professor of Oncology in the University of Nebraska Medical Center, Department of Pathology and Microbiology. Dr. Heldreth mentioned that Dr. Cohen has already become a critical part of this Panel, and he expressed his thanks to Dr. Cohen for joining his expertise.

In addition to the ingredient dossiers under review at this meeting, Dr. Heldreth encouraged the Panel to confirm their intent for future iterations of both the Inhalation Resource Document and the MOE Resource Document by vote. He also discussed plans to update the Hair Dye Epidemiology Resource Document, in light of the newly added cancer expertise that Dr. Cohen brings.

The first of CIR's four 2025-IJT issues is 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%20 Review%20(CIR)). Additionally, copies of this issue in IJT's Nxtbook format, are available here:

Feb 2025- https://www.nxtbook.com/sage/sage/ijt_cir_202502/

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 reaffirmed the conclusion reached in 1 of these safety assessments (i.e., chose not to re-open the original report). A rereview summary for this safety assessment will be prepared and presented to the Panel at a future meeting.

- Beeswax, Copernica Cerifera (Carnauba) Wax, Euphorbia Cerifera (Candelilla) Wax, and Rhus Succedanea Fruit Wax - 4 ingredients

For the other previous assessment, the Panel chose not to re-open the report, but additionally chose to split the ingredients into 2 rereview summaries: 1) in one rereview summary they reaffirmed the conclusion reached in the original report of 2 in-use ingredients, but 2) in the other, which comprised 5 ingredients with no uses, they issued a new conclusion of "use not supported." The CIR Steering Committee previous amended the Priorities so that 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; the Panel exercised this new pathway for the first time herein. Thus, 2 rereview summaries for this previous safety assessment will be prepared and presented to the Panel at a future meeting.

1. Glyceryl Isostearates and Glyceryl Stearate/Acetate - 2 ingredients, original conclusion reaffirmed
2. Glyceryl Collagenate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Maleate, and Glyceryl Thiopropionate – 5 ingredients, conclusion transmuted to use not supported

Inhalation Resource Document

The Panel reviewed the revised Inhalation Resource Document and assessed the suitability of the inhalation boilerplate (BP) language. They considered the updates and additions to accurately reflect their understanding of exposure to airborne particles and droplets resulting from the use of cosmetic sprays. The Panel examined available particle size data across various cosmetic spray categories and requested a clearer presentation of the summarized findings. Additionally, they deliberated on modifying the inhalation BP language, particularly in cases where inhalation toxicity data are absent, to better highlight potential inhalation risks associated with the use of specific cosmetic spray products. The Panel deemed these changes as editorial and agreed that the document should be posted to the CIR Resources page once the editing is complete. Once posted, stakeholders will have 60 days to comment before this version of the document is considered final.

MOE Resource Document

The Panel reviewed the updated MOE resource document and determined the preferred terminology to be used in systemic quantitative risk assessment (QRA). They conducted a comprehensive evaluation of the application and significance of the MOE approach in the safety assessment of cosmetic ingredients. Additionally, they engaged in a thorough discussion on its limitations, considering challenges, uncertainties, and areas that require further validation and characterization to enhance the scientific liability and applicability of this approach in risk assessment. The Panel decided to issue an official 60-day comment period for this document, which will be posted on CIR's website after further editorial revisions based on the meeting discussion and comments from the Council.

Draft 2026 Priorities

The CIR Procedures require preparation of the Draft 2026 Priority List for public comment by June 1, 2025. However, it is advantageous for the 2026 Draft Priority List to be issued for public comment earlier (March 2025) in the process to allow more time for the acquisition of data. The draft priority list commonly comprises nominated-for-cause ingredients and ingredients with the highest frequency of use (FOU), out of those that have yet to be reviewed by the Panel. CIR has yet to receive any nominated-for-cause ingredient proposals this year; such proposals may yet be made, as late as the September 8-9, 2025 meeting of the Panel, wherein this priorities will be finalized. FOU data are provided via FDA's RLD; for this priority setting process, RLD were received from the FDA in July 2024 (in response to a Freedom of Information Act request).

There are 15 reports proposed, covering 43 ingredients, on the 2026 Draft Priorities List. Once a proposal of a hair dye for assessment has been received from the PCPC Hair Color Technical Committee (HCTC), 16 new reports in total will be proposed for the 2026 docket. Reports previously prioritized and on the CIR docket at the end of 2025, as well as an extensive number of re-reviews of previous assessments, will supplement the total number of reports to be assessed in 2026.

Alpha-Isomethyl Ionone is the 1st ingredient on the list with nearly 12,000 formulations reported in the RLD. While this ingredient is used as a fragrance and has a published, RIFM-completed safety assessment for that use, Alpha-Isomethyl Ionone is also reported to function as a skin conditioning agent – miscellaneous. Accordingly, is the safety assessment for fragrance uses also sufficient for other cosmetic uses/exposures of

this ingredient? According to the RLD, only 3,764 of the formulations reported for this ingredient are linked to fragrance preparation categories (05), including: (a) Colognes and toilet waters, (b) Perfumes, (c) Powders (dusting and talcum) (excluding aftershave talc), and (d) Other fragrance preparations. Which function, and at what concentration, this ingredient is used for in the other 8,165 products is non-obvious. The Panel agreed that a concentration of use survey should be conducted for the non-fragrance uses of this ingredient, to inform their decision as to whether it will be reviewed hereby.

Groupings of ingredients, drafted by CIR Staff, were included in the document. Following the conclusion of the March meeting and prior to the June meeting, the Panel's Read Across Working Group (RAWG) is asked to consider the Draft Priority List and determine if any changes should be made to the groupings. If the RAWG determines that changes to the groupings should be made, time will be docketed on the June meeting agenda to discuss with the full Panel.

Scientific Literature Reviews

The following Scientific Literature Reviews (SLRs)or Notices to Proceed Without the Preparation of an SLR 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

Next Expert Panel Meeting

Monday and Tuesday, June 9 - 10, 2025, to be held ***in-person***, at the Westin Georgetown, 2350 M 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