ADMIN

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EXPERT PANEL MEETING
September 30 – October 1, 2024

Cosmetic Ingredient Review

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**MEMORANDUM**

To: The Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 170th Meeting of the Panel — Monday and Tuesday, September 30th – October 1st, 2024
Date: September 6, 2024

Welcome to the third Panel Meeting of 2024! The agenda and accompanying materials for the 170th Expert Panel Meeting, to be held on September 30th – October 1st, 2024, are now available. ***The location is the same as our meeting in June*** – and is in-person, at the Westin Georgetown, 2350 M St., NW, Washington, DC 20037. ***The meeting will start on both days at 8:30 AM EST***. The meeting is open to the public; no prior registration is required. While participation in this meeting will be exclusively in-person, audience members may view the meeting live, via MS Teams (note: there will be no option to participate in the discussions virtually). Invitations (3) to join the virtual component of the meeting may be received by request in advance of the meeting at the meeting page:

https://www.cir-safety.org/meeting/170th-expert-panel-meeting

The meeting agenda includes the consideration of 11 reports advancing in the review process, including 7 draft final reports, 1 draft tentative report, and 3 draft reports (2 of which are re-opened reviews). Also on the agenda are 5 previous reports proposed for rereview. ***For these proposed rereviews, the Panel is only being asked if the reports should be reopened.*** Additionally, a rereview summary is on the agenda for editorial review. There are also 2 administrative items, including the draft final priorities and a strategy memo on the inhalation boilerplate language.

As we continue with our efforts to reduce the quantity of late breaking information, we are making a cutoff for nearly all information sent to the Panel. The exception to this cutoff is any pertinent information relevant to a Draft Final Report. (For this meeting, the reports that fall into this category are Lanolin, 4-Amino-*m*-Cresol, MIBK, Toluene, Pentapeptides, BHA, and *t*-Butyl Alcohol.) ***Submissions received on non-final reports, after the issuance of the Wave 2 supplement on September 20th, will be held back until the next Panel review of those reports.***

As a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), FDA created the Cosmetics Direct program, which began accepting cosmetic product registrations in December 2023, with a mandatory submission deadline for manufacturers of July 1, 2024. Following the passing of this deadline, CIR submitted a FOIA request in the hopes of getting a similar dataset as that from prior requests to the VCRP. However, the content and structure of data received from Cosmetics Direct is significantly different from the VCRP. In the simplest terms, the VCRP data we received in the past were ingredient-centric, while the new Cosmetic Data are product-centric. Parsing out all of the information we need therein, and ensuring quality and confidence in the output, is still ongoing. However, we have some ***tentative*** results to share.

This dataset is massive. Close to 350,000 cosmetic products were registered in the Cosmetics Direct database between December 18, 2023 and July 10, 2024 (the data snapshot time CIR received in response to the FOIA request). Side-by-side comparisons of 2023-VCRP and 2024-Cosmetics Direct data demonstrate greater ingredient FOU values in Cosmetics Direct than from VCRP, not surprisingly considering that MoCRA made product registrations mandatory. However, the increased values are also

due, in some small part, to brand duplicates (e.g., one distinct product formulation sold under 20 brand names might inadvertently count as 20 uses). Table 1 provides a comparison of VCRP FOU totals and ***tentative*** FOU totals from Cosmetics Direct, for some of the ingredients under review at this meeting. ***Please note, these FOU values from the Cosmetics Direct database are the result of a simple text-based search of how many entries include the relevant ingredient name.***

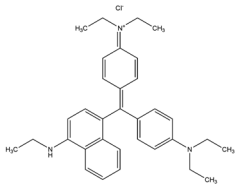
Table 1. Ingredients Assessed at this Meeting: FOU from Cosmetics Direct and VCRP

| Ingredient | Frequency of Use (FOU) | |
|---|---|---|
| | 2024 Cosmetic Direct | 2023 VCRP |
| 2,4-Diaminophenoxyethanol HCl | 4469 | 93 |
| 4-Amino-*m*-Cresol | 1221 | 28 |
| 2-Bromo-2-Nitropropane-1,3-Diol | 167 | 36 |
| Acetylated Lanolin Alcohol | 252 | 2 |
| Ascorbic Acid | 17057 | 1267 |
| Basic Blue 7 | 29 | 1 |
| BHA | 470 | 70 |
| Cholesterol | 3007 | 494 |
| Diisopropanolamine | 21 | 1 |
| Hydrogenated Castor Oil | 5634 | 501 |
| Isopropanolamine | 318 | 3 |
| Lanolin | 2654 | 266 |
| Lanolin Alcohol | 657 | 65 |
| Lanolin Oil | 526 | 39 |
| Palmitoyl Pentaptide-4 | 1936 | 239 |
| PEG-75 Stearate | 5559 | 1844 |
| PEG-100 Stearate | 1233 | 97 |
| Propylene Carbonate | 13551 | 882 |
| Ricinus Communis (Castor) Seed Oil | 7433 | 1018 |
| Sodium Ascorbyl Phosphate | 2004 | 355 |
| Sodium Ascorbate | 507 | 32 |
| *t*-Butyl Alcohol | 745 | 136 |
| Toluene | - | - |

Deriving ingredient FOU by category is less straightforward in terms of coding, and we are continuing to sort that out. However, the categories data utilization faces an even bigger challenge: there has been no vetting of the application of one or more categories appropriately to a product. In one example, a product sold as a bath bomb was categorized in Cosmetics Direct by the submitter as a bubble bath, a lotion, and a moisturizer; that in turn puts each ingredient in that product under these 3 use categories. We will continue to sort the data and seek help from our colleagues at the FDA to remedy these issues.

**Draft Reports - There are 3 draft reports for review. Sufficient data to proceed, or issue an Insufficient Data Announcement (IDA)?**

1. Basic Blue 7 – DR (Christina) – ***Dr. Belsito reports on day 2*** – This is the first time the Panel is reviewing a safety assessment on this ingredient. In June 2024, CIR issued a Scientific Literature Review (SLR) Notice to Proceed (NTP) for Basic Blue 7 because an intensive search of information in the published scientific literature, online databases, and other sources on this ingredient provided insufficient information to justify the preparation of a formal SLR. Under European regulations for cosmetic ingredients, Basic Blue 7, when used as a substance in hair dye products, is categorized in Annex II, the list of substances prohibited in cosmetic products in Europe.

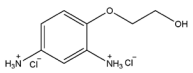


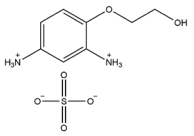
   The other data identified in the published literature were information on non-cosmetic uses. No unpublished data were received.

   According to 2023 VCRP survey data, Basic Blue 7 was reported to be used in 1 nail polish and enamel product. However, in the Cosmetics Direct data we received, 29 products listed Basic Blue 7 as an ingredient. No uses of this ingredient were reported in a concentration of use survey submitted by the Personal Care Products Council in 2023.

   The Panel should consider the lack of information available on which to base a safety assessment of this ingredient, specify the data needed to complete the assessment, and issue an IDA.

2. 2,4-Diaminophenoxyethanol HCl – DAR (Christina) – ***Dr. Cohen reports on day 2*** – In 1991, the Panel published a safety assessment on 2,4-Diaminophenoxyethanol HCl (previously named 2,4-Diaminophenoxyethanol Dihydrochloride) with the conclusion that, "2,4-Diaminophenoxyethanol Dihydrochloride is safe as a cosmetic ingredient in the present practices of use and concentration." In 2007, the Panel issued a Final Amended Report, that also included the sulfate salt ingredient, with the conclusion that these ingredients are safe as hair dye ingredients in the practices of use and concentration described in that report. Because more than 15 years have passed since the Panel last reviewed this report (and because the 2007 report was never published), it is now time to review these ingredients again to update the information and then publish this amended safety assessment on 2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate.





   According to 2023 VCRP survey data, 2,4-Diaminophenoxyethanol HCl is reported to be used in 93 formulations. The majority of these uses are in hair coloring preparations; however, uses have been reported for eye makeup preparations. Ten uses were reported for 2,4-Diaminophenoxyethanol Sulfate; 1 of these uses is reported in an eye makeup preparation. The frequencies of use for 2,4-Diaminopheoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate have only slightly changed since these ingredients were last reviewed by the Panel. In 2006, 2,4-Diaminophenoxyethanol HCl was reported in the VCRP to be used in 115 formulations and 2,4-Diaminophenoxyethanol Sulfate was reported to be used in 5 formulations. At that time, all uses for both ingredients were reported to be in hair coloring formulations.

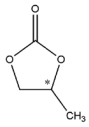
   Based on the data we received, 2,4-Diaminophenoxyethanol HCl is listed as an ingredient in 4,469 products registered in Cosmetics Direct. One hundred fifty-one products registered in the Cosmetics Direct database listed 2,4-Diaminophenoxyethanol Sulfate as an ingredient.

   The results of the concentration of use survey conducted by the Council in 2022 indicate 2,4-Diaminophenoxyethanol HCl has a maximum concentration of use range of 0.56 - 2.4% in hair dyes. 2,4-Diaminophenoxyethanol Sulfate has a maximum concentration of use range of 0.25 - 0.35% in hair dyes. In the 2007 amended report, the maximum concentration of use range for 2,4-Diaminophenoxyethanol HCl was 0.05 - 2% in hair dyes; the sulfate salt was reported to be used at a maximum concentration of 0.4 - 2% in hair dyes. (The 2% is the final on-head concentration after mixing with hydrogen peroxide for both ingredients).

   If no further data are needed, the Panel should formulate an updated Discussion and issue a Tentative Amended Report. However, if additional data are required, the Panel should be prepared to identify those

needs and issue an IDA.

3. Propylene Carbonate – DAR (Priya) – ***Dr. Belsito reports on day 2*** – In 1987, the Panel published a safety assessment on Propylene Carbonate with the conclusion that Propylene Carbonate is safe as a cosmetic ingredient in the present practices of use and concentration, as stated in that report. The Panel previously considered a re-review of this ingredient in 2004 and re-affirmed the 1987 conclusion, as published in 2006. Since it had been at least 15 years since the previous re-review, the Panel again considered a re-review of this ingredient in March 2023, and determined to re-open the report due to increased frequency and concentration of use.



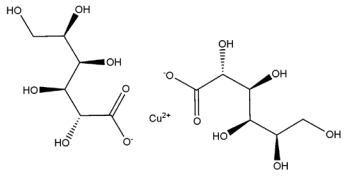
According to 2023 VCRP survey data, Propylene Carbonate is reported to be used in 882 total formulations. According to 2024 Cosmetics Direct data, this ingredient is reported to be used in 13,551 total formulations. The results of the concentration of use survey conducted by the Council in 2022 indicate that this ingredient is used at up to 17.9% in leave-on formulations. In 2002/2003, this ingredient was reported to be used in 178 formulations, at up to 5%.

Unpublished data have been received and incorporated into this report. These data include: 1) a human patch test, 5-d clinical use assay, and clinical use test on a serum containing 17.84% Propylene Carbonate, and 2) a maximization assay in human skin using a product containing 17.84% Propylene Carbonate.

If no further data are needed, the Panel should formulate an updated Discussion and issue a Tentative Amended Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an IDA.

**Draft Tentative Report - There is 1 draft tentative report for consideration. Issue a tentative conclusion?**

1. Copper Gluconate – TR (Preethi) – ***Dr. Cohen reports on day 2*** – This is the second time the Panel has seen a safety assessment of this ingredient. At the March 2024 meeting, the Panel issued an IDA. The Panel identified the following data needs to determine the safety of this ingredient:

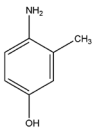


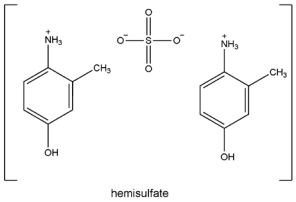
- Impurities data for Copper Gluconate as used in cosmetics
- Dermal irritation and sensitization data at maximum concentration of use
- Ocular irritation data, if available

Numerous data submissions were received in response to the IDA and have been incorporated into the report. After reviewing these documents, the Panel should issue a Tentative Report with a safe, safe with qualifications, insufficient, unsafe, or split conclusion, and Discussion items should be identified.

**Draft Final Reports - There are 7 Draft Final Reports for consideration. Review these drafts, especially the rationale provided in the Discussion sections, and issue final reports, as appropriate.**

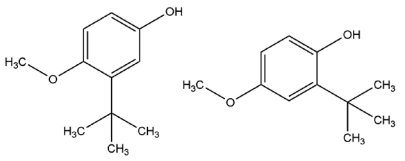
1. 4-Amino-*m*-Cresol – FAR (Christina) – ***Dr. Cohen reports on day 2*** – At the March 2024 meeting, the Panel issued a Tentative Amended Report with the conclusion that 4-Amino-*m*-Cresol is safe for use as a hair dye ingredient in the present practices of use and concentration described in this safety assessment. No additional data have been received for this report. Comments provided by the Council on the Tentative Amended Report have been addressed.






The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Amended Report.

2. BHA – FAR (Preethi) – ***Dr. Cohen reports on day 2*** – At the June 2023 meeting, the Panel decided to reopen the safety assessment of BHA to evaluate potential endocrine and reproductive effects of BHA at high doses and to provide an updated review of this ingredient. Upon reviewing the Draft Amended Report at the March 2024 meeting, the Panel concluded that any developmental and reproductive, endocrine, androgenic, and estrogenic effects that were observed were seen primarily in cell systems and at non-physiological concentrations. Additionally, the Panel considered the exposure assessment of BHA in foods helpful in providing a context for safety. Consequently, the Panel issued a Tentative Amended Report with the conclusion that BHA is safe in cosmetics in the present practices of use and concentration.



3-(*tert*-butyl)-4-methoxyphenol 2-(*tert*-butyl)-4-methoxyphenol

Since the March 2024 meeting, CIR has not received any additional data. Comments were received from the Council on the Tentative Amended Report, and we seek the Panel's input on a number of points raised therein. Additionally, the exposure assessment section has been revised since the March 2024 meeting, mainly, to utilize the appropriate retention factor and product exposure values for estimation, as mentioned in a recommended reference paper.

The Panel should carefully review the revised exposure assessment section and the Abstract, Discussion, and Conclusion, and issue a Final Amended Report.

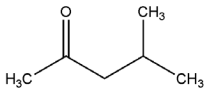
3. Lanolin – FAR (Christina) – ***Dr. Belsito reports on day 2*** - At the March 2024 meeting, the Panel issued a Tentative Amended Report with the conclusion that Lanolin and 8 lanolin-derived ingredients included in this report are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Since the March 2024 meeting, no additional unpublished data have been submitted for these ingredients. One new reference has been identified in an updated literature search; the data provided in this reference are additive information on retrospective patch test studies in children.

Comments provided by the Council on the Tentative Amended Report have been addressed. However, in the comments, the Council asked for the revision of the following sentence from the Discussion: "Suppliers and users of these ingredients must accept responsibility for assuring that these ingredients are risk-free." The Council also noted that it is not clear why this sentence is needed. This sentence is part of the boilerplate language on transmission of infectious disease for the Discussion section of reports. The Panel should review this language and determine if an update to this boilerplate, as well as the statements made in the Discussion, are appropriate.

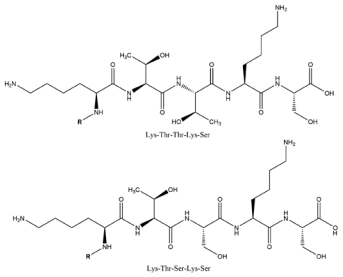
The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Amended Report.

4. MIBK – FAR (Thushara) – ***Dr. Belsito reports on day 2*** - At the December 2023 meeting the Panel concluded MIBK is safe as used in nail care products and as an alcohol denaturant in nail polish removers. However, at the March 2024 Panel meeting, due to the absence of recent use information regarding the broad area of nailcare, the Panel decided to reaffirm their previous conclusion of 2004. The Panel concluded that MIBK is safe as used in nail polish removers (as opposed to nail care products) and as an alcohol denaturant in cosmetics in the present practices of use and concentrations described in this safety assessment.



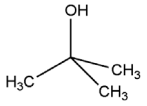

No new data have been received since the March 2024 Panel meeting, nor were comments received on the revised Tentative Amended Report. The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Amended Report.

5. Pentapeptides – FR (Preethi) – ***Dr. Belsito reports on day 2*** - At the March 2024 meeting, the Panel considered negative human irritation and sensitization data and the limited dermal penetration of Palmitoyl Pentapeptide-4, further supported by log p values for all 3 ingredients. Consequently, the Panel issued a Tentative Report for public comment with the conclusion that Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 (KTTKS and KTSKS sequences) are safe in cosmetics in the present practices of use and concentration described in the safety assessment.




Since the March 2024 meeting, no new data were received. Comments that were received from the Council for the Tentative Report have been addressed. The Panel should carefully review the revised exposure assessment section, Abstract, Discussion, and Conclusion and issue a Final Report.

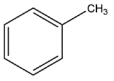
6. *t*-Butyl Alcohol – FAR (Preethi) – ***Dr. Belsito reports on day 2*** - At the March 2024 meeting, the Panel determined that a negative guinea pig maximization test mitigated the need for confirmatory sensitization data at the maximum concentration of use, and that the weight-of-evidence did not support a carcinogenic effect. In agreement with the Discussion from the 2005 amended report, the Panel considered the developmental effects of *t*-Butyl Alcohol secondary to maternal toxicity, resulting from maternal milk and not in utero exposure. Consequently, the Panel issued a Tentative Amended Report with the conclusion that *t*-Butyl Alcohol is safe as used in cosmetics.




Comments that were received from the Council for the Tentative Amended Report have been addressed. On May 6, 2024, the CIR Science and Support Committee (CIR SSC) submitted comments on dose metrics for exposure calculations in CIR reports, referencing the *t*-Butyl Alcohol report. The comments included a table of estimated dermal exposure to a product containing 0.125% *t*-Butyl Alcohol based on several patch types typically used in an HRIPT. The CIR SSC reiterates that "because the dermal dose used in an HRIPT is usually higher than the dermal dose resulting from product use, an HRIPT on the product with the maximum use concentration is not necessary." Accordingly, Table 5 in this report has been updated to reflect these dermal exposure dose metrics in mg/cm$^2$. Furthermore, the CIR SSC noted the 1% *t*-Butyl Alcohol in a liquid diet used in a mouse study actually resulted in a dose of about 8000 mg/kg/d, whereas the approximately 0.91% maximum use concentration in an aftershave resulted in a systemic exposure of only 0.26 mg/kg/d.

The Panel should carefully review the revised exposure assessment section and the Abstract, Discussion, and Conclusion and issue a Final Amended Report.

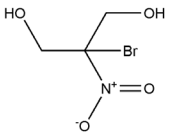
7. Toluene – FAR (Priya) – ***Dr. Cohen reports on day 2*** - According to 2023 VCRP data, Toluene has 0 reported uses. (According to 2024 Cosmetics Direct data, Toluene was not listed as an ingredient in any products.) However, according to the use survey conducted by the Council in 2022 - 2023, Toluene is reported to be used at up to 20% nail products. Toluene was previously reported to be used in other products at low concentrations; however, updated concentration of use information was received verifying that these reported concentrations are due to residual amounts of Toluene in cosmetics, and not intentional uses.




Council's comments cited the EPA's oral reference dose (RfD) of 0.08 mg/kg/d, which is derived from an endpoint of increased kidney weight with an uncertainty factor of 3000 applied. As the endpoints that the Panel have concerns about are DART and neurological effects, this RfD has not been used in the MOS calculation. Another EPA inhalation reference concentration (RfC) of 5 mg/m$^3$, referenced by the Council, has been applied in the MOS calculation because it is derived from human occupational data for the endpoint of neurologic effects, and has been adjusted for continuous exposure (24 h/d). However, since it is an inhalation concentration limit, an additional conversion from inhalation concentration to oral dose has been performed. ***The Panel is asked to determine whether EPA's oral RfD of 0.08 mg/kg/d should be used as the point of departure (POD) for the MOS calculation, and to evaluate the validity of an additional MOS calculation that uses the RfC as the POD, incorporating a conversion from inhalation concentration to oral dose.***

The Panel should carefully review the revised exposure assessment section and Abstract, Discussion, and Conclusion and issue a Final Amended Report.

**Abbreviated Rereview (i.e., rereview proposal) – There are 5 rereview documents. Because it has at least been 15 years since the previous review was published, in accordance with CIR Procedures, the Panel is only being asked if the report should be reopened.**

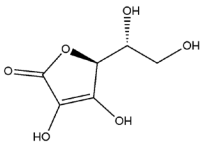
1. 2-Bromo-2-Nitro-1,3-Propanediol – RR (Thushara) – ***Dr. Cohen reports on day 2*** – 

The Panel first published a review of the safety of 2-Bromo-2-Nitropropane-1,3-Diol in 1980. The Panel concluded that it was safe as a cosmetic ingredient at concentrations up to and including 0.1% except under the circumstance where its action with amines or amides can result in the formation of nitrosamines or nitrosamides. An addendum to the report was published in 1984 due to the availability of new test data; the Panel reaffirmed their 1980 conclusion, and further stated that the additional data suggested the possibility that upon absorption, 2-Bromo-2-Nitropropane-1,3-Diol could contribute to the endogenous formation of nitrosamines in humans. The Panel previously considered a re-review of this report in 2004/2005 and reaffirmed the conclusion, as published in 2006.

   In August 2024, an extensive search of the world's literature was performed for studies dated 2000 forward. A historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are provided in the dossier. Studies on chemistry, dermal absorption, toxicology, genotoxicity, dermal irritation and sensitization, pharmacological effects, several clinical studies, and case reports were found as a result of the updated search. Some of this information is similar to the previous reports, while some provide distinctly new data.

   According to 2023 VCRP data, 2-Bromo-2-Nitropropane-1,3-Diol is reported to be used in 36 cosmetic formulations, as opposed to 1 use reported in 2003. (According to 2024 Cosmetics Direct data, 2-Bromo-2-Nitropropane-1,3-Diol was listed as an ingredient in 167 products.) The maximum reported concentration of use has decreased. According to a 2023 Council survey, the maximum reported concentration of use is 0.05% (in hand wipes (a leave-on) and eye make remover); in 2003, the maximum reported concentration of use was 0.1% (in eye shadow, blushers, and lipsticks).

   If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a full Draft Amended Report will be presented at an upcoming meeting.

2. Ascorbic Acid – RR (Preethi) – ***Dr. Cohen reports on day 2*** - 

The Panel first published a review of the safety of Ascorbic Acid (previously called L-Ascorbic Acid), Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate as Used in Cosmetics in 2005. The Panel concluded based on the available data contained in the report that these ingredients were safe as used in cosmetic products.

   In August 2024, an extensive search of the world's literature was performed for studies dated 2000 forward. A historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed herein. Studies evaluating the in vitro dermal penetration of Ascorbic Acid and Magnesium Ascorbyl Phosphate were found. A human dermal irritation study, photoprotective studies, an in vitro ocular irritation study, and a case report were also found for Ascorbic Acid. Additionally, acute toxicity studies, in vitro genotoxicity studies, dermal irritation and sensitization studies, and ocular irritation studies for both Magnesium Ascorbyl Phosphate and Sodium Ascorbyl Phosphate, a short-term oral toxicity study for Sodium Ascorbyl Phosphate, and a photoprotective study for Magnesium Ascorbyl Phosphate were found. An in vitro anti-carcinogenicity study and a dermal sensitization study were found for Sodium Ascorbate.

   Ascorbic Acid is reported to be used in 1267 formulations according to 2023 VCRP data (according to 2024 Cosmetics Direct data, Ascorbic Acid was listed as an ingredient in 17,057 products), while it was reported to be used in only 431 formulations in 2001; Sodium Ascorbyl Phosphate has the second highest reported use in 355 formulations and had 0 uses reported in the 2001 VCRP data. Ascorbic Acid was reported to be used at up to 10% in face and neck and body and hand products in 2000; in 2023, the maximum reported concentration of use for Ascorbic Acid increased to 17% in skin fresheners. Sodium Ascorbyl Phosphate was reported to be used at 3% in moisturizing and night products in 2000; in 2023, Sodium Ascorbyl Phosphate was reported to be used at a maximum reported concentration of 2% in non-spray moisturizing products. Ascorbic Acid and Sodium Ascorbyl Phosphate have higher reported concentrations of use in products that come in contact with mucous membranes (lipsticks and cleansing products, respectively), and both have newly reported use in baby products; Ascorbic Acid, Sodium Ascorbate, and Sodium Ascorbyl

Phosphate have greater reported concentrations of use for products used near the eye.

If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a full Draft Amended Report will be presented at an upcoming meeting.

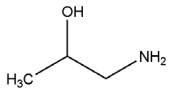
3. Castor Oil – RR (Preethi) – ***Dr. Belsito reports on day 2*** - The Panel first published a review of the safety of Ricinus Communis (Castor) Seed Oil and Ricinoleates, in 2007. The Panel concluded that Ethyl Ricinoleate, Glycol Ricinoleate, Hydrogenated Castor Oil, Methyl Ricinoleate, Potassium Ricinoleate, Ricinoleic Acid, Ricinus Communis (Castor) Seed Oil and Sodium Ricinoleate are safe as cosmetic ingredients in the practices of use and concentrations as described in the safety assessment. Six other ingredients that were originally a part of this group have since been reviewed with other ingredient groups. Namely, Cetyl Ricinoleate, Isopropyl Ricinoleate, and Octyldodecyl Ricinoleate have been reviewed with the Alkyl Esters, Glyceryl Ricinoleate and Ricinoleate SE have been reviewed with Monoglyceryl Monoesters, and Zinc Ricinoleate has been reviewed with Zinc Salts.

In August 2024, an extensive search of the world's literature was performed for studies dated 2002 forward. New data were found, including data pertaining to FDA-approved uses in food contact surfaces and as inactive ingredients in drugs, a dermal absorption study of Ricinoleic Acid, and dermal and oral absorption studies of Ricinus Communis (Castor) Seed Oil in humans.

According to data received from the VCRP, reported frequency of use has significantly increased for both Hydrogenated Castor Oil (202 uses in 2002 to 501 uses in 2023) and Ricinus Communis (Castor) Seed Oil (769 uses in 2002 to 1018 uses in 2023). (According to 2024 Cosmetics Direct data, these two ingredients were listed as ingredients in 5,634 and 7,433 products, respectively.) According to industry surveys from the Council, maximum reported concentrations of use have decreased for Hydrogenated Castor Oil from a maximum of 39% in other eye makeup preparations in 2002 to a maximum of 21% in eyebrow pencils in 2023. Ricinus Communis (Castor) Seed Oil was reported to be used at a maximum of 81% in lipsticks in 2002, and was reported to be used at a maximum of 77.8% in moisturizing products in 2023. Ricinoleic Acid and Sodium Ricinoleate did not have reported concentrations of use in the previous or present review. Ethyl Ricinoleate, Glycol Ricinoleate, Methyl Ricinoleate, and Potassium Ricinoleate continue to not have reported frequencies or concentrations of use.

If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a full Draft Amended Report will be presented at an upcoming meeting.

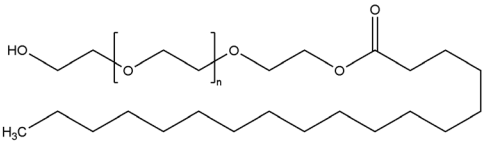
4. Isopropanolamines – RR (Preethi) – ***Dr. Cohen reports on day 2*** - The Panel first published a review of the safety of Diisopropanolamine, Triisopropanolamine, Isopropanolamine, and Mixed Isopropanolamines in 1987, concluding that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration (as described in the safety assessment); these ingredients should not be used in products containing *N*-nitrosating agents. The Panel previously considered a re-review of this report December 2004 and re-affirmed the 1987 conclusion, as published in 2006.




In August 2024, an extensive search of the world's literature was performed for studies dated 2001 forward. Numerous, mostly cumulative, studies were found for these ingredients and included for review. Also included for your review are current and historical use data. Overall, the reported frequency and concentrations of use for these ingredients have decreased. In 2002, according to the VCRP, Diisopropanolamine was reported to be used in 33 formulations, while Diisopropanolamine had 1 use reported in 2023. (According to 2024 Cosmetics Direct data, these two ingredients were listed as ingredients in 318 and 21 products, respectively.) The maximum reported concentrations of use, according to industry surveys by the Council, in 2004 were 1% Isopropanolamine in hair dyes and colors and 1% Triisopropanolamine in a pump hair spray; the maximum reported concentration of use in 2023 was 0.85% Triisopropanolamine in non-spray tonics, dressings, and other hair grooming aids.

If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a full Draft Amended Report will be presented at an upcoming meeting.

5. PEG Stearates – RR (Preethi) – ***Dr. Belsito reports on day 2*** - The Panel first published a review of the safety of ten PEG Stearates in 1983. The Panel concluded, on the basis of the available information presented in the report, that PEG-2, -6, -



8, -12, -20, -32, -40, -50, -100, and -150 Stearates are safe as cosmetic ingredients in the present practices of concentration and use. The Panel previously considered a re-review of this report in November 2002 and re-affirmed the 1983 conclusion, as published in 2005. At that time, 20 more PEG Stearate ingredients were added to this group (PEG-3, -4, -5, -6-32, -7, -9, -10, -14, -15, -18, -23, -25, -30, -35, -36, -45, -55, -75, -90, and -120 Stearates).

In August 2024, an extensive search of the world's literature was performed for studies dated 2000 forward. Non-cosmetic uses for multiple PEG Stearates, an in vitro study evaluating the effect of PEG-8, -12, and -40 Stearate on penetration enhancement, and an in vitro ocular irritation study on PEG-2 Stearate were found.

Reported frequency and concentrations of use mostly decreased or remained constant for these ingredients, with a few exceptions. Frequency of use, according to data from the VCRP, significantly increased for PEG-75 and PEG-100 Stearate, which were reported to be used in 1844 and 97 formulations in 2023, respectively, compared to 424 and 6 reported uses in 2002, respectively. (According to 2024 Cosmetics Direct data, these two ingredients were listed as ingredients in 5559 and 1233 products, respectively.) As reported in industry surveys conducted by the Council, the maximum reported concentration of use increased for PEG-20 Stearate, from 4% (in body and hand and in moisturizing products) in 2002 to 10.1% (in tonics, dressings, and other hair grooming aids) in 2023. Several exposure type categories were newly reported in 2023; namely, PEG-2 Stearate was reported to be used in 5 lipstick formulations. In 2023, newly reported uses near the eye included PEG-45 Stearate in 3 eyeliner formulations and at up to 3.2% in mascara and PEG-75 Stearate was reported to be used in 3 eye shadow formulations (concentration of use not reported) and at up to 1% in eye lotions. PEG-40, PEG-75, and PEG-100 Stearate were reported to be used at up to 0.6, 0.75, and 1.4% in the baby lotions, oils, powders, and creams category, respectively; PEG-8 Stearate was reported to have 3 uses in baby lotions, powders, and creams (concentrations of use not reported). PEG-30 Stearate and PEG-150 Stearate were reported to be used at 0.2 and 0.7%, respectively in baby shampoos.

If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a full Draft Amended Report will be presented at an upcoming meeting.

**Administrative Item - there are 3 administrative item.**

1. Inhalation – SM (Jinqiu) – ***Dr. Cohen reports on day 2*** – Enclosed is a strategy memo for the Panel's review regarding an update of the inhalation boilerplate language. The Panel last approved the CIR Resource Document – Respiratory Exposure to Cosmetic Ingredient – at the December 2021 meeting. Subsequent revisions were made at the December 2023 meeting to incorporate new findings on particle size distribution in certain propellant-based sprays, such as dry shampoos in powdered galenic formulations. These updates highlighted the necessity to modify the inhalation boilerplate to accurately reflect the Panel's perspective on the associated inhalation risks.
2. Final Priorities – Admin (Bart) – ***Dr. Belsito reports on day 2*** - There are 18 reports docketed, covering 32 ingredients, on the 2024/2025 drat Final Priorities List. While the priority list includes only the lead ingredients, groupings of ingredients for reports can be found on the following pages therein. Additionally, potential rereviews for the coming year are stated.
3. Cholesterol – RRSum (Preethi) – ***Dr. Belsito reports on day 2*** - The Panel reviewed frequency (2023) and concentration of use (2022) data, in addition to any new, available, and relevant safety data. Considering this information, as well as the information provided in the original safety assessment and the prior re-review document, the Panel chose not to reopen the report, and instead reaffirmed the 1986 conclusion.

**Full Panel Meeting**

The Panel will consider the 7 reports to potentially be issued as Final Reports, followed by the remaining reports advancing in the process (i.e., the Tentative Report and Draft Reports). In addition, a consensus should be reached for each of the 5 rereview documents, a rereview summary, priorities and the inhalation boilerplate strategy memo.

***Please remember, the meeting starts at 8:30 AM EST on day 1 and day 2***.

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

# Agenda
# 170th Meeting of the Expert Panel for Cosmetic Ingredient Safety
# September 30th – October 1st, 2024

**Monday, September 30, 2024**

| | | |
|---|---|---|
| **8:30 AM** | **WELCOME TO THE 170th EXPERT PANEL TEAM MEETINGS** | **Drs. Bergfeld/Heldreth** |
| **8:45 AM** | **TEAM MEETINGS** | **Drs. Belsito/Cohen** |

**Dr. Belsito's Team***

| | |
|---|---|
| FAR (CB) | 4-Amino-*m*-Cresol |
| FAR (CB) | Lanolin |
| DR (CB) | Basic Blue 7 |
| DAR (CB) | 2,4-Diaminophenoxyethanol HCl |
| FAR (TD) | MIBK |
| RR (TD) | 2-Bromo-2-Nitro-1,3-Propanediol |
| Admin (MF\|BH) | Priorities |
| SM (JZ) | Inhalation |
| FAR (PC) | Toluene |
| DAR (PC) | Propylene Carbonate |
| FR (PR) | Pentapeptide ingredients |
| FAR (PR) | BHA |
| FAR (PR) | *t*-Butyl Alcohol |
| TR (PR) | Copper Gluconate |
| RR (PR) | Castor Oil |
| RR (PR) | Ascorbic Acid |
| RR (PR) | PEG Stearates |
| RR (PR) | Isopropanolamines |
| RRSum (PR\|MF\|BH) | Cholesterol |

**Dr. Cohen's Team**

| | |
|---|---|
| FR (PR) | Pentapeptide ingredients |
| FAR (PR) | BHA |
| FAR (PR) | *t*-Butyl Alcohol |
| TR (PR) | Copper Gluconate |
| RR (PR) | Castor Oil |
| RR (PR) | Ascorbic Acid |
| RR (PR) | PEG Stearates |
| RR (PR) | Isopropanolamines |
| RRSum (PR\|BH\|MF) | Cholesterol |
| Admin (MF\|BH) | Priorities |
| FAR (CB) | 4-Amino-*m*-Cresol |
| FAR (CB) | Lanolin |
| DR (CB) | Basic Blue 7 |
| DAR (CB) | 2,4-Diaminophenoxyethanol HCl |
| FAR (TD) | MIBK |
| RR (TD) | 2-Bromo-2-Nitro-1,3-Propanediol |
| SM (JZ) | Inhalation |
| FAR (PC) | Toluene |
| DAR (PC) | Propylene Carbonate |

**The purpose of the Cosmetic Ingredient Review and the Expert Panel for Cosmetic Ingredient Safety is to determine those cosmetic ingredients for which there is a reasonable certainty, in the judgment of competent scientists, that the ingredients are safe under intended conditions of use.**

**FR: Final Report || FAR: Final Amended Report || TR: Tentative Report || TAR: Tentative Amended Report || DR: Draft Report || DAR: Draft Amended Report || RR: Re-Review || RRsum: Re-Review Summary || Rev: Revised || SM: Strategy Memo || Admin: Administrative item**

**BH: Bart Heldreth || MF: Monice Fiume || CB: Christina Burnett || PC: Priya Cherian || TD: Thushara Diyabalanage || PR: Preethi Raj || JZ: Jinqiu Zhu**

*Team moves to the breakout room.

| Tuesday, October 1, 2024 | | | |
|---|---|---|---|
| **8:30 AM** | **WELCOME TO THE 170th FULL EXPERT PANEL MEETING** | | **Dr. Bergfeld** |
| **8:40 AM** | Admin **MINUTES OF THE JUNE 2024 EXPERT PANEL MEETING** | | **Dr. Bergfeld** |
| **8:45 AM** | **DIRECTOR'S REPORT** | | **Dr. Heldreth** |
| **9:00 AM** | **FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS** | | |
| | **Final Reports** | | |
| | FAR (CB) | Lanolin – ***Dr. Belsito reports*** | |
| | FAR (CB) | 4-Amino-*m*-Cresol – ***Dr. Cohen reports*** | |
| | FAR (TD) | MIBK – ***Dr. Belsito reports*** | |
| | FAR (PC) | Toluene – ***Dr. Cohen reports*** | |
| | FR (PR) | Pentapeptide ingredients – ***Dr. Belsito reports*** | |
| | FAR (PR) | BHA – ***Dr. Cohen reports*** | |
| | FAR (PR) | *t*-Butyl Alcohol – ***Dr. Belsito reports*** | |
| | **Reports Advancing** | | |
| | TR (PR) | Copper Gluconate – ***Dr. Cohen reports*** | |
| | DR (CB) | Basic Blue 7 – ***Dr. Belsito reports*** | |
| | DAR (CB) | 2,4-Diaminophenoxyethanol HCl – ***Dr. Cohen reports*** | |
| | DAR (PC) | Propylene Carbonate – ***Dr. Belsito reports*** | |
| | **Other Items** | | |
| | RR (TD) | 2-Bromo-2-Nitro-1,3-Propanediol – ***Dr. Cohen reports*** | |
| | RR (PR) | Castor Oil – ***Dr. Belsito reports*** | |
| | RR (PR) | Ascorbic Acid – ***Dr. Cohen reports*** | |
| | RR (PR) | PEG Stearates – ***Dr. Belsito reports*** | |
| | RR (PR) | Isopropanolamines– ***Dr. Cohen reports*** | |
| | RRSum (PR) | Cholesterol – ***Dr. Belsito reports*** | |
| | SM (JZ) | Inhalation Boilerplate – ***Dr. Cohen reports*** | |
| | Admin (BH) | Priorities (Final) – ***Dr. Belsito reports*** | |

**ADJOURN** – *The next will be held virtually on Monday and Tuesday,* ***December 2 – 3, 2024****. Please check the CIR website for details as the meeting approaches, and to register to attend.*

**On the basis of all data and information submitted, and after following all of the Procedures (https://www.cir-safety.org/supplementaldoc/cir-procedures), the Expert Panel shall determine whether each ingredient, under each relevant condition of use, is safe, safe with qualifications, unsafe, or there are insufficient data or information to make a determination of safety. Upon making such a determination, the Expert Panel shall issue a conclusion and/or announcement.**

**FR: Final Report || FAR: Final Amended Report || TR: Tentative Report || TAR: Tentative Amended Report || DR: Draft Report || DAR: Draft Amended Report || RR: Re-Review || RRsum: Re-Review Summary || Rev: Revised || SM: Strategy Memo || Admin: Administrative item**

**BH: Bart Heldreth || MF: Monice Fiume || CB: Christina Burnett || PC: Priya Cherian || TD: Thushara Diyabalanage || PR: Preethi Raj || JZ: Jinqiu Zhu**

# ONE HUNDRED SIXTY-NINTH MEETING

# OF THE

# EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

June 3-4, 2024

Westin Georgetown
2350 M St., NW
Washington, DC 20037

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairperson

Donald V. Belsito, M.D., Teamleader

David E. Cohen, M.D., Teamleader

Curtis D. Klaassen, Ph.D.

Allan E. Rettie, Ph.D.

David Ross, Ph.D.

Thomas J. Slaga, Ph.D.

Paul W. Snyder, D.V.M., Ph.D.

Susan Tilton, Ph.D.

Liaison Representatives

Consumer

Courtney Griffin, J.D.

Industry

Alex Kowcz, M.B.A.

Government

Hong Xie, Ph.D.

Jannavi Srinivasan, Ph.D.

Prashiela Manga, Ph.D.

Janet Zang, Ph.D.

_____
Adopted (Date)

_____
Wilma F. Bergfeld, M.D.

## CIR Staff

Administration
Bart Heldreth, PhD - Executive Director

Monice Fiume, MBA - Senior Director

Carla Jackson - Administrative Coordinator

Subject Matter Expertise
Jinqiu Zhu, PhD, DABT, ERT, DCST - Toxicologist

Analysis
Christina L. Burnett, MSES - Senior Scientific Analyst

Priya Cherian, MS - Senior Scientific Analyst

Preethi S. Raj, MS - Senior Scientific Analyst

Thushara Diyabalanage, Ph.D.–Senior Scientific Analyst

Information Services
Kevin Stone Fries, MLS - Information Services Manager

**Other Meeting Attendees**

| *Name* | *Organization* |
|---|---|
| David Allen | ICCS |
| Yunqi An | Victoria's Secret & Co. |
| Jennifer Ator | Tox Services |
| John Bailey | EAS Consulting Group |
| Don Bjerke | Procter & Gamble |
| AJ Cuevas | Combe |
| Carol Eisenmann | Personal Care Products Council |
| Tom Myers | Personal Care Products Council |
| Jeffrey Nicolai | Performance Beauty Group |
| Kimberly Norman | Personal Care Products Council |
| Pushpa Rao | ANR RegTox Consulting LLC |
| Prajakta Shimpi | L'Oreal USA |
| Kathy Stanton | Personal Care Products Council |
| Patra Volarath | US FDA |

## CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 169th meeting of the Expert Panel for Cosmetic Ingredient Safety. She announced that over 6,000 ingredients have been reviewed by the Panel. At this meeting, Dr. Bergfeld noted that the Panel reviewed 14 ingredient reports, including 3 finals, 1 tentative, 4 draft reports, and 6 re-reviews. Dr. Bergfeld thanked the CIR staff for their continuing work in presenting high-quality documents to the Panel and for their responses to public comments. Additionally, Dr. Bergfeld thanks the Personal Care Products Council and the CIR Science and Support Committee for their great input. She also thanked Dr. David Allen and Mr. Tom Myers for their presentations to the Panel on the first day of the meeting. Dr. Bergfeld also noted the work being performed by the Read-Across Working Group and issues that the Panel has reviewed concerning exposure and risk assessment and strategies for ingredients such as phthalates.

Dr. Bergfeld discussed a recommendation to be made to the CIR Steering Committee that the Panel should have the ability to determine if an ingredient should be immediately categorized as "use not supported." Reviews of ingredients that have no uses and with obvious potential hazards could be expeditiously given a conclusion of use not supported by the Panel without two years of waiting.

## APPROVAL OF MINUTES

The minutes of the March 28 - 29, 2024 (168th) Expert Panel meeting were approved.

## 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 National Center for Biotechnology Information (NCBI) of the National Library of Medicine (NLM), an institute within the US National Institutes of Health (NIH) for their gracious efforts in linking the Panel's ingredient safety assessments to the chemical monographs in PubChem. PubChem is a public chemical database at the NCBI with millions of users every month. This linking profoundly increases the free accessibility and visibility of the Panel's work to users around the world. Dr. Heldreth noted a special thank you to Pertti (Bert) J. Hakkinen, Ph.D., F-SRA, "NIH Special Volunteer" in Toxicology and Environmental Health Sciences, NCBI – NIH, for spearheading the inclusion of CIR as a freely available data source.

## FINAL SAFETY ASSESSMENTS

### 1,2,4-Trihydroxybenzene

The Panel issued a Final Report with the conclusion that 1,2,4-Trihydroxybenzene is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment.

1,2,4-Trihydroxybenzene is reported to function as an oxidative hair dye in hair coloring products. The Panel noted that 1,2,4-Trihydroxybenzene is categorized in Annex II, the list of substances prohibited in cosmetic products in Europe, when used as a substance in hair and eyelash dye products. The Scientific Committee on Consumer Safety (SCCS) does not consider 1,2,4-Trihydroxybenzene safe, due to potential genotoxicity when used as an auto-oxidative hair dye component in permanent hair dye formulations. In vitro genotoxicity studies yielded mixed results and although in vivo micronucleus tests have yielded negative results, the European Union cannot accept the results of the in vivo studies because of their ban on animal testing. Conversely, the Panel considered the results of these in vivo studies, along with the negative results for other toxicity endpoints, slow absorption through the skin, and the fact that enzymes present in the skin deactivate harmful reactive oxygen species following dermal exposure, and concluded that these mitigated any concerns with the mixed in vitro genotoxicity findings.

The Panel also noted that 1,2,4-Trihydroxybenzene is a potent suicide substrate of tyrosinase, i.e., the action of tyrosinase on 1,2,4-Trihydroxybenzene may cause the enzyme to self-inactivate. As tyrosinase is a key enzyme involved in the synthesis of the pigment melanin; the inactivation of tyrosinase by 1,2,4-Trihydroxybenzene may play a role in skin depigmentation. The Panel noted that depigmentation is considered to be a drug effect in the US and should not occur during the use of cosmetic products. Accordingly, cosmetic formulators should only use 1,2,4-Trihydroxybenzene in products in a manner that does not cause depigmentation.

### Yeast-Derived Ingredients

The Panel issued a Final Report with a split conclusion of safety for these 56 yeast-derived ingredients. Ingredients in which sufficient dermal sensitization data and a food use/generally recognized as safe (GRAS)/qualified presumption of safety (QPS) status were available, are considered safe in the present practices of use and concentration described in the assessment; these 18 ingredients comprise:

Galactomyces Ferment Filtrate
Hydrolyzed Candida Saitoana Extract
Hydrolyzed Metschnikowia Agaves Extract*
Hydrolyzed Metschnikowia Reukaufii Extract*
Hydrolyzed Torulaspora Delbrueckii Extract*
Metschnikowia Agaves Extract*
Metschnikowia Reukaufii Lysate Extract
Phaffia Rhodozyma Extract*
Phaffia Rhodozyma Ferment Extract*
Pichia Anomala Extract
Pichia Minuta Extract*
Saccharomyces Cerevisiae Extract
Torulaspora Delbrueckii Extract*
Torulaspora Delbrueckii Ferment*
Yarrowia Lipolytica Extract*
Yarrowia Lipolytica Ferment Lysate*
Yarrowia Lipolytica Oil*
Yeast Ferment Extract

Also considered safe were 21 generic yeast-derived ingredients (ingredients in which the species of yeast used in manufacturing was not provided in the Dictionary), when derived from species of yeast included in the report with sufficient dermal sensitization data and a food use/GRAS/QPS status. These yeast species include: *Candida magnoliae, Candida oleophila, Candida saitoana, Metschnikowia agaves, Metschnikowia reukaufii, Pichia anomala, Pichia minuta,*

*Pichia naganishii, Phaffia rhodozyma, Saccharomyces cerevisiae, Saccharomyces pastorianus, Torulaspora delbrueckii*, and *Yarrowia lipolytica*, when used in the manufacturing of the following ingredients:

Hydrolyzed Saccharomyces Cell Wall*
Hydrolyzed Saccharomyces Extract*
Hydrolyzed Saccharomyces Lysate Extract*
Hydrolyzed Yeast
Hydrolyzed Yeast Extract
Lactic Yeasts*
Pichia Extract*
Saccharomyces*
Saccharomyces Extract
Saccharomyces Ferment
Saccharomyces Ferment Extract*
Saccharomyces Ferment Extract Lysate Filtrate
Saccharomyces Ferment Filtrate
Saccharomyces Ferment Lysate Extract*
Saccharomyces Ferment Lysate Filtrate
Saccharomyces Lysate
Saccharomyces Lysate Extract
Saccharomyces Lysate Extract Filtrate*
Saccharomyces Lysate Filtrate
Yeast
Yeast Extract

**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.*

It should be noted that data are deemed insufficient to conclude on the safety of the generic ingredients listed above when the species used to manufacture these ingredients do not have dermal sensitization data and food use/GRAS/QPS status. Finally, the data were also considered insufficient to make a determination of safety for the following 17 ingredients:

Hydrolyzed Candida Bombicola Extract**
Hydrolyzed Kluyveromyces Extract**
Hydrolyzed Metschnikowia Shanxiensis**
Kluyveromyces Extract
Lipomyces Lipid Bodies**
Lipomyces Oil**
Lipomyces Oil Extract**
Metschnikowia Henanensis Extract**
Metschnikowia Viticola Extract**
Pichia Caribbica Ferment**
Pichia Ferment Extract Filtrate**
Pichia Ferment Lysate Filtrate
Pichia Heedii Extract**
Pichia Pastoris Ferment Filtrate**
Schizosaccharomyces Ferment Extract Filtrate**
Schizosaccharomyces Ferment Filtrate
Schizosaccharomyces Pombe Extract**

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

Both systemic toxicity data (via a 28-d dermal toxicity assay; food use/GRAS/QPS status may be used in lieu of systemic toxicity data) and dermal sensitization data are needed to conclude on the safety of these ingredients. It should be noted that if 28-d dermal toxicity data are provided, and data indicate absorption of the ingredient, other toxicity endpoints would be required to determine safety (e.g., developmental and reproductive toxicity).

## TENTATIVE SAFETY ASSESSMENTS

### Inositol

The Panel issued a Tentative Report for public comment 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 US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) survey and 2022 concentration of use survey data, this ingredient is used in 212 formulations and at up to 2%. The safety of this ingredient is supported by its robust data profile, GRAS status, endogenous nature, low concentrations of use, and lack of positive alerts in various toxicological studies. The Panel noted reproductive effects in an oral study performed in mice; however, the Panel determined that the effects observed in this study were irrelevant to cosmetic use as the doses in this assay were much higher than what would result via cosmetic exposure.

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

The Panel issued a Revised Tentative Amended Report for public comment with the conclusion that *p*-Phenylenediamine, *p*-Phenylenediamine HCl, and *p*-Phenylenediamine Sulfate* are safe for use as hair dye ingredients in the present practices of use and concentration described in the safety assessment. However, the Panel also concluded that these ingredients are unsafe for use in dermal coloring applications, specifically noting unsafe use in temporary black henna tattoos.

*Not reported to be in current use. If this ingredient not in current use was to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.

*p*-Phenylenediamine, *p*-Phenylenediamine HCl, and *p*-Phenylenediamine Sulfate are reported to function as oxidative hair dyes in hair coloring products. Positive genotoxicity results were observed in several in vitro studies but were not observed in studies performed in vivo. Although mixed results were reported in the genotoxicity studies, the Panel noted the dose-dependent nature and an NOAEL of 8 mg/kg/d in a 90-d oral study, the negative results in developmental and reproductive toxicity and carcinogenicity studies, the protective margin of safety values, and the short consumer exposure time to these ingredients in hair dye formulations. Because the Panel recognizes the potential for dermal sensitization to these ingredients, and that some persons may be sensitized under intended conditions of use. The Panel stated that the final on-head concentration of use in hair dye products be limited to 1%; the safety conclusion does not apply to on-head concentrations greater than 1%.

It is highly inappropriate for this ingredient to be used in products other than 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 US 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 ingredient.

In addition, the Panel noted that use of *p*-Phenylenediamine has been reported in eye makeup preparations. The Panel reiterates that the FD&C Act mandates that color additives must be approved by the FDA for their intended use before they are used. *p*-Phenylenediamine is not an approved color additive in cosmetics products, and thereby, use in eye makeup products is not permitted. 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.

## INSUFFICIENT DATA ANNOUNCEMENTS

### *Paeonia suffruticosa*-Derived Ingredients

The Panel issued an IDA for the following 5 *Paeonia suffruticosa*-derived ingredients.

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

The Panel requires the following information to determine the safety of these ingredients:

- 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 includes the root bark of the plant
- For Paeonia Suffruticosa Seed Oil
  - Clarification on ingredient constituents
- 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 ingredients:
  - 28-d dermal toxicity assay
    - if positive, data on systemic toxicity endpoints (e.g., developmental and reproductive toxicity)
  - Genotoxicity data
- For all ingredients, except Paeonia Suffruticosa Root Extract
  - Dermal irritation and sensitization data

### 4-Chloro-2-Aminophenol

The Panel issued an IDA for 4-Chloro-2-Aminophenol. The additional data needed to determine safety for this hair dye ingredient are:

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

### Fatty Monocarboxylates

The Panel reviewed the Revised Draft Report on these 11 fatty amphocarboxylates, along with consideration of potential read-across sources, and issued an IDA. In order to conclude on the safety of these ingredients, the Panel requested the following data:

- Dermal absorption data
- Developmental and reproductive toxicity data on Disodium Cocoamphodiacetate
- Further information regarding the composition and impurities of these ingredients as used in cosmetics (particularly percentage of actives in ingredients, fatty acid compositions, and degrees of esterification (e.g., how much of Sodium Cocoamphoacetate has 0, 1, or 2 acetate substitutions)
- Sensitization data on Sodium Lauroamphoacetate and Disodium Lauroamphodiacetate at maximum use concentrations
- The Panel's Read-Across Working-Group (RAWG) intends to again assess read-across strategies for these ingredients
  - Any information (e.g., clarifications on compositions) to support the use of the read-across sources provided in the meeting draft, is requested.

## TABLED REPORT

**Prostaglandin Analogues**

The Panel reviewed the Draft Tentative Report on the prostaglandin analogues Isopropyl Cloprostenate and Ethyl Tafluprostamide and determined to table the report for the timely receipt of incoming data. These data include:

- Data on Ethyl Tafluprostamide:
  - Receptor binding potency studies
  - In vitro neutral red uptake assays
  - ReproTracker assay
  - ToxProfiler assay
  - In silico endocrine receptor/activation predictions
  - Literature research on endocrine receptor activation by analogues
  - Analysis of differences in metabolism due to germinal fluorine atoms in the suitability of analogues in read-across analyses
  - Report on read-across analyses
- Data on Isopropyl Cloprostenate:
  - QSAR assessment
  - Dermal metabolism and penetration assay
  - Independent ophthalmological analysis on ocular parameters (e.g., colorimetry) observed in clinical assay
- The Panel's RAWG intends to again assess read-across strategies for these ingredients
  - Any information to support the use of the read-across sources, provided in the meeting draft, is requested.

In addition, the Panel requested information regarding the potential receptors associated with the prostaglandin analogues reviewed in this report along with binding/potency/Ki values. Furthermore, the Panel requested sufficient data to demonstrate that under conditions of cosmetic use these ingredients would not the elicit any "drug-like" effects (as the safety of drugs is outside of their purview).

## 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 4 reports should be reopened; a Draft Amended Report will be presented to the Panel for each of these safety assessments at a later meeting.

- Butoxyethanol – 1 ingredient
- Boric Acid – 2 ingredients
- Potassium Cocoyl Hydrolyzed Collagen – 2 ingredients
- Propyl Gallate – 1 ingredient (with the request to include other relevant alkyl gallate ingredients)

The Panel reaffirmed the conclusion reached for 1 of these safety assessments (i.e., chose to not re-open the original report). A re-review summary will be presented to the Panel at an upcoming meeting.

- Cholesterol - 1 ingredient

## PRESENTATIONS

Dr. David Allen, Senior Director of Human Health Sciences and Operations at the International Collaboration on Cosmetics Safety (ICCS), delivered an insightful presentation titled "Identifying Eye Irritation Hazards Without Using Animals." The presentation covered various non-animal testing methods and models, along with OECD-defined approaches and the EPA's decision framework for hazard identification of eye irritation. The presentation is available on the meeting page, or directly here: https://www.cir-safety.org/sites/default/files/CIR_eye%20irritation_03Jun2024v2.pdf.

Tom Myers, President and CEO of the Personal Care Products Council (PCPC), also spoke to express his sincere gratitude to the Panel and CIR staff for their efforts over that last almost-50 years to ensure consumer safety, utilizing sound science and their years of expertise. He also remarked on PCPC's dedication to supporting the modernization efforts of CIR and the safety evaluation process of cosmetic ingredients.

## MoE vs MoS

The Panel reviewed comments from the CIR Science and Support Committee (SSC) concerning the differentiation between the terms Margin of Exposure (MoE) and Margin of Safety (MoS). The Panel noted that in the scientific literature MoS and MoE are often used interchangeably, and discussed the key parameters in conducting quantitative risk assessment (QRA), such as the transparency in determining Point of Departure (POD) and the application of uncertainty or extrapolation factors in exposure assessment and protective margin calculations. The Panel considers when MoE is used in quantitative risk assessments of reports, clarifications should be provided to explain the use of safety assessment factors that account for inter- and intra-species differences and exposure duration. Additionally, the Panel requested the definitions used in QRA be easily accessible through the resource document portal on the CIR website.