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Memo

Agenda

Minutes

EXPERT PANEL MEETING
March 6-7, 2023

Cosmetic Ingredient Review

Commitment & Credibility since 1976

MEMORANDUM

To: The Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 164th Meeting of the Expert Panel — Monday and Tuesday, March 6th-7th, 2023
Date: February 10, 2023

Welcome to the first Panel Meeting of 2023! The agenda and accompanying materials for the 164th Expert Panel Meeting, to be held on March 6-7, 2023, are now available. Please note that this meeting is on a ***Monday and Tuesday***. The location is ***new*** – this meeting will be held virtually via the Microsoft Teams platform. Invitations (3) to join the meeting will arrive separately in your email inbox. Panel members and liaisons will be registered automatically. However, other interested parties may register to attend in advance of the meeting at the meeting page:

https://www.cir-safety.org/meeting/164th-expert-panel-meeting

At this meeting we would like to honor the memory of beloved past Director of CIR, Dr. F. Alan Andersen. Alan joined the US FDA in 1971 and worked there until 1993. In 1993, he became Director of CIR and retired from that position in 2013. After retiring, he continued by consulting through EAS. Throughout his career, Alan was a champion for public health and was always a pleasure to work with. Alan passed away on December 2, 2022. He is survived by his devoted wife of 47 years, Linda, his five children, and three grandchildren. He will be greatly missed.

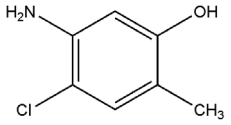
The meeting agenda includes the consideration of 12 reports advancing in the review process, including 7 final reports, 1 tentative report, and 4 draft reports. Also on the agenda are 11 rereview documents (6 proposals for rereview and 5 rereview summaries). ***In each case of a rereview proposal, the Panel is only being asked if the report should be reopened; in each case of a rereview summary, the Panel is only being asked to provide editorial comments.*** Additionally, there are 2 administrative documents, a Hair Dye Epidemiology update prepare by Jinqiu and the Draft 2024 Priorities.

In addition, the team meetings on Day 1 will kick-off with 2 speakers from the Council, Thomas F. Myers (Executive Vice President, Legal & Regulatory Affairs) and Karin Ross (Executive Vice President, Government Affairs), who will brief the Panel on the Modernization of Cosmetics Regulation Act of 2022 (MoCRA).

Team Meetings

Draft Report - There are 4 draft reports for review. - Sufficient data to proceed, or issue an IDA?

1. 5-Amino-4-Chloro-*o*-Cresol – DAR (Christina) – ***Dr. Cohen reports on day 2*** - The Panel previously reviewed the safety of 5-Amino-4-Chloro-*o*-Cresol in an assessment that was published in 2004. In June 2022, the Panel determined to reassess the safety of this ingredient. In the original report, the Panel concluded that 5-Amino-4-Chloro-*o*-Cresol is safe as used in oxidative and non-oxidative (semi-permanent) hair dyes.

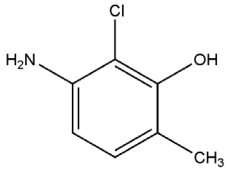


   Much of the data on 5-Amino-4-Chloro-*o*-Cresol in the original report was actually on the salt ingredient, 5-Amino-4-Chloro-*o*-Cresol HCl. This hair dye ingredient has been added to this amended report because in situ and in formulation the salt and free base are identical.

   According to 2022 VCRP survey data, 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl have no reported uses. The results of the concentration of use survey conducted by the Council in 2021 for the free base also report no uses for this ingredient. A survey is currently underway for the HCl salt. When the original safety assessment was published in 2004, 5-Amino-4-Chloro-*o*-Cresol was reported to have no uses, according to 1998 VCRP data. However, according to industry survey data submitted in 1994, 5-Amino-4-Chloro-*o*-Cresol was reported to be used at up to 1% in hair dyes and colors in combination with hydrogen peroxide. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use are presented both cumulatively by likely duration and exposure and individually by product category.

   If no further data are needed to reach a conclusion of safety, the Panel should formulate a 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 Insufficient Data Announcement (IDA).

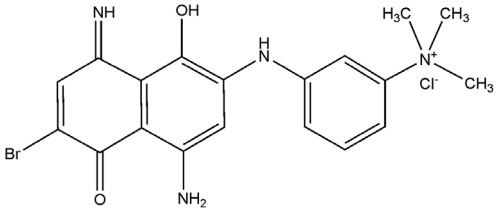
2. 5-Amino-6-Chloro-o-Cresol – DAR (Christina) – ***Dr. Belsito reports on day 2*** – The Panel previously reviewed the safety of 5-Amino-6-Chloro-*o*-Cresol (along with 5-Amino-4-Chloro-o-Cresol above) in an assessment that was published in 2004. In June 2022, the Panel determined to reassess the safety of this ingredient. In the original report, the Panel concluded that 5-Amino-6-Chloro-*o*-Cresol is safe as used in oxidative and non-oxidative (semi-permanent) hair dyes.



   According to 2022 VCRP survey data, 5-Amino-6-Chloro-*o*-Cresol has 27 reported uses in hair coloring products. The results of the concentration of use survey conducted by the Council in 2021 reported that 5-Amino-6-Chloro-*o*-Cresol is used at up to 0.24% in hair dyes and colors. When the original safety assessment was published in 2004, 5-Amino-6-Chloro-*o*-Cresol was reported to have no uses, according to 1998 VCRP data. However, according to industry survey data submitted in 1996, 5-Amino-6-Chloro-*o*-Cresol was reported to be used at up to 2% in hair dyes and colors. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use are presented both cumulatively by likely duration and exposure and individually by product category.

   If no further data are needed to reach a conclusion of safety, the Panel should formulate a 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. Basic Blue 99 – DAR (Christina) – ***Dr. Cohen reports on day 2*** - The Panel previously reviewed the safety of Basic Blue 99 in an assessment that was published in 2007. In December 2022, the Panel determined that this safety assessment should be re-opened for re-evaluation due to concerns regarding the variability of the composition of the ingredient. In the original report, the Panel concluded that Basic Blue 99 is safe as a hair dye ingredient.

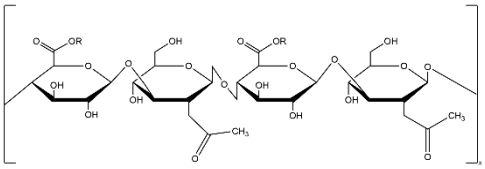


According to 2022 VCRP survey data, Basic Blue 99 has 38 reported uses; however, non-hair dye uses have been reported, including 1 use in nail polish and enamel and 6 uses in non-coloring hair products. The results of the concentration of use survey provided by the Council in 2022 indicated this ingredient is used in hair dyes at a maximum concentration of 0.2%. When the original safety assessment was published in 2004, Basic Blue 99 was reported to have 51 uses in hair coloring products. In 2002, the maximum concentration of use for Basic Blue 99 in hair coloring products was reported to be 2%. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use is presented both cumulatively by likely duration and exposure and individually by product category.

Since the December meeting, no new data have been submitted. If no further data are needed to reach a conclusion of safety, the Panel should formulate a 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.

4. Hyaluronates – DR (Priya) – ***Dr. Belsito reports on day 2*** – This is the first time the Panel is seeing a safety assessment of these 7 hyaluronate cosmetic ingredients.

Hyaluronic Acid
Hydrolyzed Calcium Hyaluronate
Hydrolyzed Hyaluronic Acid
Hydrolyzed Sodium Hyaluronate
Potassium Hyaluronate
Sodium Acetylated Hyaluronate
Sodium Hyaluronate



Sodium Acetylated Hyaluronate and Hydrolyzed Hyaluronic Acid were included on the 2022 Priority List due to reported frequencies of use. It was noted that 3 related ingredients previously reviewed by the Panel in a report published in 2009 (Hyaluronic Acid, Potassium Hyaluronate, and Sodium Hyaluronate) would soon be considered for re-review. Accordingly, the Panel deemed it appropriate to include the 3 previously-reviewed ingredients in this new safety assessment. (The Panel had concluded that these 3 ingredients are safe in cosmetics in the present practices of use and concentration, as described in that 2009 safety assessment.)

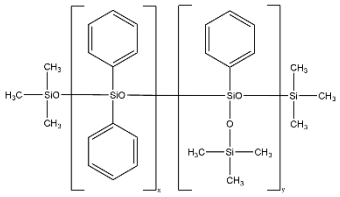
The Scientific Literature Review (SLR) on this group of 7 hyaluronate ingredients was announced on October 5, 2022. Since the issuing of the SLR, unpublished data have been received including manufacturing, composition and impurities, genotoxicity, developmental and reproductive toxicity, dermal irritation, dermal sensitization, phototoxicity, and ocular irritation data.

According to 2022 FDA VCRP data, Sodium Hyaluronate has the highest frequency of use (4048 total formulations; 3680 leave-on formulations, 366 rinse-off formulations, and 2 formulations diluted for bath use). This use of this ingredient has increased significantly since it was last reviewed; it was reported to be used in 601 formulations in 2005. All other ingredients are reported to be used in 568 formulations or less. The results of the 2021 concentration of use survey conducted by the Council indicate Sodium Hyaluronate also has the highest concentration of use; it is used at up to 7.5% in face and neck products (not spray). As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use are presented both cumulatively by likely duration and exposure and individually by product category.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report. If the available data are insufficient, the Panel should issue an IDA specifying the data needs therein.

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

1. Phenyl-Substituted Methicones – TR (Preethi) – ***Dr. Cohen reports on day 2*** – This is the second time the Panel is seeing a safety assessment of these 7 cosmetic ingredients. At the September 2022 meeting, a Draft Report was presented to the Panel. Upon review, the Panel issued an IDA for the following data needs:



   - Method of manufacture data and impurities (specific to cosmetic ingredients) for all ingredients
   - Molecular weight ranges for all ingredients

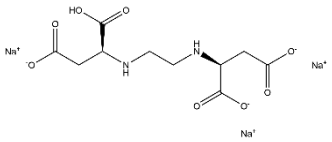
   The following data were received in response to the IDA and have been incorporated into the current iteration of the report: method of manufacturing, molecular weights, impurities data, results of repeated insult patch tests (a lip balm containing 11% Diphenylsiloxy Phenyl Trimethicone and a product containing 20% Phenyl Trimethicone), and a process flow diagram.

   As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use are presented both cumulatively by likely duration and exposure and individually by product category.

   A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider these items, discuss the data (or lack thereof), and issue a Tentative Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

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

1. Trisodium Ethylenediamine Disuccinate – FR (Priya) – ***Dr. Belsito reports on day 2*** – At the September 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that Trisodium Ethylenediamine Disuccinate and Tetrasodium Iminodisuccinate are safe in cosmetics in the present practices of use and concentration described in the safety assessment.



   No unpublished data were submitted since the issuing of the Tentative Report. Comments on the Tentative Report that were received from Council have been addressed. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use are presented both cumulatively by likely duration and exposure and individually by product category. After carefully reviewing the Abstract, Discussion, and Conclusion, the Panel should be prepared to issue a Final Report.

2. *Rosa centifolia* – FR (Regina) – ***Dr. Cohen reports on day 2*** – At the September 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that the following 9 *Rosa centifolia*-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

   Rosa Centifolia Bud Extract
   Rosa Centifolia Flower
   Rosa Centifolia Flower Extract
   Rosa Centifolia Flower Juice
   Rosa Centifolia Flower Oil
   Rosa Centifolia Flower Powder
   Rosa Centifolia Flower Water
   Rosa Centifolia Flower Wax
   Rosa Centifolia Stem Extract

   The Panel also concluded the available data are insufficient to make a determination of safety for the following 3 *Rosa centifolia*-derived ingredients under the intended conditions of use in cosmetic formulations:

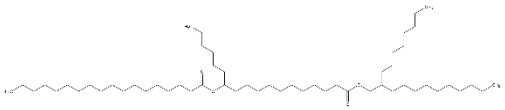
Rosa Centifolia Callus Culture Extract
Rosa Centifolia Extract
Rosa Centifolia Leaf Cell Extract

The additional data needed to determine safety for these 3 ingredients are:

- Method of manufacturing
- Composition and impurities data
- Dermal irritation and sensitization data
- Dermal toxicity (28-day dermal)
    - If positive, other toxicological endpoints (e.g., developmental and reproductive toxicity, genotoxicity, carcinogenicity, etc.) may be needed.

No additional data were submitted. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use for each ingredient is presented both cumulatively by likely duration and exposure and individually by product category. The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

3. Octyldodecyl Stearoyl Stearate – FAR (Regina) – ***Dr. Belsito reports on day 2*** – At the December 2022 meeting, the Panel issued a Draft Tentative Amended Report for public comment with the conclusion that Octyldodecyl Stearoyl Stearate is safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

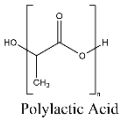


No additional data were submitted. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use for each ingredient is presented both cumulatively by likely duration and exposure and individually by product category. 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.

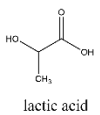
4. Mallow – FR (Preethi) – ***Dr. Cohen reports on day 2*** – This is the second time the Panel is seeing a safety assessment of these 8 mallow-derived cosmetic ingredients. At the December 2022 meeting, a Draft Report was presented to the Panel. The Panel acknowledged that the confirmed use of mallow as a food mitigated systemic toxicity concerns. Additionally, negative findings in human dermal irritation and sensitization studies on the Malva Sylvestris (Mallow) Flower/Leaf/Stem Extract and Malva Sylvestris (Mallow) Flower Extract reassured the Panel of safety. The Panel noted the presence of constituents (e.g., cinnamal) which are possible sensitizers, though at levels below concern for these individual ingredients. Accordingly, the Panel issued a Tentative Report for public comment with the conclusion that the 8 *Malva sylvestris* (Mallow)-derived ingredients are safe in cosmetic in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

No additional data were submitted. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use for each ingredient is presented both cumulatively by likely duration and exposure and individually by product category. The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

5. Polyhydroxystearic Acid – FR (Preethi) – ***Dr. Belsito reports on day 2*** – This is the second time the Panel is seeing a safety assessment of these 3 cosmetic ingredients. At the September 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that Polyhydroxystearic Acid, Poly(3-Hydroxyoctanoic Acid), and Polylactic Acid are safe in cosmetics in the present practices of use and concentration described in the safety assessment.



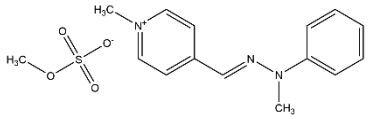
Polylactic Acid



lactic acid

No additional data were submitted. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use for each ingredient is presented both cumulatively by likely duration and exposure and individually by product category. The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

6. Basic Yellow 87 – FR (Christina) – ***Dr. Cohen reports on day 2*** –



At the December 2022 meeting, the Panel issued a Tentative Report with the conclusion that Basic Yellow 87 is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment. The Panel noted that Basic Yellow 87 has been reported to be used in 4 non-coloring cosmetic products. The Federal FD&C Act mandates that color additives must be approved by the FDA for their intended use before they are used. Basic Yellow 87 is an unapproved color additive in cosmetics products, and thereby, such use is not permitted. Furthermore, non-hair dye use is not within the purview of this Panel.
No additional data were submitted. As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use for each ingredient is presented both cumulatively by likely duration and exposure and individually by product category. The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

7. Clays – FAR (Christina) – ***Dr. Belsito reports on day 2*** – At the September 2022 meeting, the Panel issued a Tentative Amended Report with the conclusion that Kaolin is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the remaining 7 naturally-sourced clay ingredients are safe in cosmetics in the present practices of use and concentration, with the exception that the available data are insufficient to make a determination of safety for these ingredients in products that may be incidentally inhaled.

No additional data were submitted. However, data that CIR staff discovered in a literature search for Illite have been incorporated into the report and highlighted to aid the Panel's review.
As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use for each ingredient is presented both cumulatively by likely duration and exposure and individually by product category. 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.

Abbreviated Rereviews (i.e., rereview proposals) – There are 6 rereview documents – In each case, the Panel is only being asked if the report should be reopened.

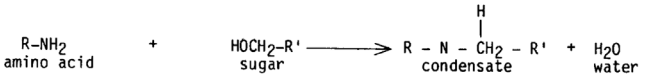
1. Wild Yam – RR (Preethi) – ***Dr. Belsito reports on day 2*** – The Panel first published a review of the safety of Dioscorea Villosa (Wild Yam) Root Extract in 2004, with a conclusion that this ingredient is safe for use in cosmetic products. In the Discussion of that report, the Panel further clarified that this conclusion is valid only for extracts prepared in a manner that produces a similar chemical profile as that described in the safety assessment, particularly in regard to diosgenin (i.e., an expected upper limit of 3.5%). Additionally, the Panel stated that extracts not prepared in a manner that produces a similar chemical profile would be considered safe if they have a similar safety test profile. Because it has been at least 15 years since it was finalized, in accord with CIR Procedures, the Panel should consider whether the safety assessment of should be re-opened.

An extensive search of the world's literature was performed for studies dated 1999 forward. A historical overview, comparison of original and new use data, search strategy, and relevant data found are enclosed with the report. Notable findings include 2 short-term oral toxicity studies and a 13-wk oral toxicity study in which the NOAEL for both rat sexes was determined to be the maximum received dose of 5000 mg/kg/d. Additionally, studies demonstrating the potential cytotoxicity of Dioscorea Villosa (Wild Yam)

Root Extract against breast cancer cell lines, anti-inflammatory effects, and a clinical study in which no significant side-effects or metabolic/endocrinal changes were seen with the 3-mo topical application of wild yam cream in healthy premenopausal women, were found.

The frequency and concentration of use is presented both cumulatively by likely duration and exposure and individually by product category. Since this report was first reviewed, the reported frequency of use has increased from 1 to 43 uses; however, the reported concentration of use has decreased. The maximum reported use concentration of Dioscorea Villosa (Wild Yam) Root Extract in 1999 was 15% (0.5% maximum solids from wild yam) in moisturizing formulations; in 2022, this ingredient is reported to be used at 0.3% in non-spray moisturizing products.

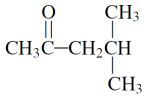
If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, conforming to the original conclusion, will be presented at an upcoming meeting.

2. Polyamino Sugar Condensate – RR (Preethi) – ***Dr. Cohen reports on day 2*** – 

The Panel first published a review of the safety of Polyamino Sugar Condensate in 1982. On the basis of the available animal data and limited human experience presented in the report, the Panel concluded that in the present practices of use and concentration (described in the safety assessment), Polyamino Sugar Condensate is safe for topical application to humans. The Panel previously considered a re-review of this report and reaffirmed the 1982 conclusion, as published in 2005. Because it has been at least 15 years since it was finalized, in accord with CIR Procedures, the Panel should consider whether the safety assessment of should be re-opened.

An extensive search of the world's literature was performed for studies dated 2000 forward. No relevant published data were found. The frequency and concentration of use are presented both cumulatively by likely duration and exposure and individually by product category. According to 2022 FDA VCRP data, Polyamino Sugar Condensate has 1 reported use in a body and hand formulation. At the time this ingredient was last considered for re-review, 25 uses were reported. Concentration of use data were neither reported during the last review nor in response to a survey conducted by the Council in 2022.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, conforming to the original conclusion, will be presented at an upcoming meeting.

3. MIBK – RR (Regina) – ***Dr. Belsito reports on day 2*** – 

The Panel first published a review on the safety of MIBK in 2004. The Panel concluded that MIBK is safe as used in nail polish removers and as an alcohol denaturant in cosmetic products. Because it has been 15 years since the previous re-review was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of MIBK should be re-opened.

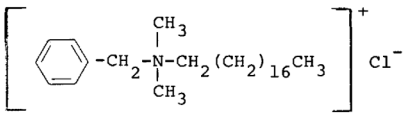
An exhaustive search of the world's literature was performed for studies dated 2000 forward. New toxicological studies were found for several endpoints (metabolism, excretion, dermal and oral toxicity, reproductive toxicity, carcinogenicity, dermal irritation, and ocular irritation). Of note, a carcinogenicity study has been completed by the National Toxicology Program (NTP). At the time of the original (2004) review no studies on the carcinogenic potential of MIBK were found, but the Panel was aware of an ongoing NTP carcinogenicity study on MIBK.

The frequency and concentration of use are presented both cumulatively by likely duration and exposure and individually by product category. The frequency of use for MIBK has decreased from 2 to 1, according to 2002 and 2022 VCRP data, respectively. The maximum reported concentration of use of this ingredient was 21% in 2003; in the April 2022 Council concentration of use survey, no uses were reported.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, conforming to the original conclusion, will

be presented at an upcoming meeting.

4. Stearalkonium Chloride – RR (Priya) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Stearalkonium Chloride in 1982, with the conclusion that Stearalkonium Chloride is safe when incorporated in cosmetic products in concentrations similar to those presently marketed.



The Panel previously considered a re-review of this report and re-affirmed the 1982 conclusion, as published in 2003. Because it has been at least 15 years since the previous re-review was published, in accord with the Procedures, the Panel should consider whether the safety assessment of Stearalkonium Chloride should be re-opened.

An extensive search of the world's literature was performed for studies dated 1999 forward. An historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed with the report.

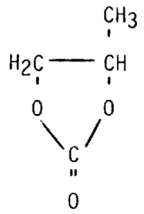
New studies were found for several toxicological endpoints (ADME, acute toxicity, DART, genotoxicity, dermal irritation, and ocular irritation). These studies were found in an ECHA dossier on Stearalkonium Chloride that referenced read-across test substances for much of the data. These data have been included in the new data document.

It should be noted that according to European Union (EU), Stearalkonium Chloride is used in rinse-off hair products, and ready-to-use preparations should not contain more than 0.3% (as benzalkonium chloride). Final product concentrations of benzalkonium chloride, bromide, and saccharinate with an alkyl chain of C14 or less must not exceed 0.1% (as benzalkonium chloride). EU restrictions also state that when using this ingredient for purposes other than inhibiting the development of microorganisms, the purpose must be apparent from the presentation of the product, and concentrations must not exceed 0.1% (as benzalkonium chloride, when used as a preservative). In addition, according to the US FDA, Stearalkonium Chloride is safe for use as a food additive, anti-microbial agent, adhesive, and slimicide (under certain restrictions).

The frequency and concentration of use is presented both cumulatively by likely duration and exposure and individually by product category. The frequency and concentration of use of Stearalkonium Chloride has decreased since this ingredient was last considered for re-review. According to 2022 frequency of use and concentration of use data, Stearalkonium Chloride is used in 88 formulations at up to 3.8%; in 2001, it was reported to be used in 151 formulations at up to 7%.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, conforming to the original conclusion, will be presented at an upcoming meeting.

5. Propylene Carbonate – RR (Priya) – ***Dr. Belsito reports on day 2*** – The Panel first published a review of the safety of Propylene Carbonate in 1987, with the conclusion that this ingredient 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 report and reaffirmed the 1987 conclusion, as published in 2006. Because it has been 15 years since the previous re-review was published, in accord with the Procedures, the Panel should consider whether the safety assessment of Propylene Carbonate should be re-opened.



An extensive search of the world's literature was performed for studies dated 1999 forward. A historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed with the report.

New toxicological studies were found for several toxicological endpoints (metabolism, dermal penetration, dermal and oral toxicity, reproductive toxicity, genotoxicity, carcinogenicity, dermal irritation, and ocular irritation). In addition, a case report was found on a patient experiencing pruritic erythematous scaly plaques with a positive patch test to a mixture containing Propylene Carbonate. It should be noted that Propylene Carbonate is used at up to 5% as an inactive ingredient in an FDA-

approved topical drug formulation.

The frequency and concentration of use is presented both cumulatively by likely duration and exposure and individually by product category. Since this ingredient was last considered for re-review, the frequency of use for Propylene Carbonate has significantly increased from 178 uses reported in 2002 to 911 uses reported in 2022. In addition, the concentration of use for this ingredient has also increased significantly. In 2003, Propylene Carbonate was reported to be used at up to 5%. According to 2022 concentration of use data, Propylene Carbonate is used at up to 17.9% (in night products (not spray)). It should be noted that Propylene Carbonate is now reported to be used in baby products (concentration of use not reported for these uses).

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, conforming to the original conclusion, will be presented at an upcoming meeting.

6. Sweet Almond – RR (Christina) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Prunus Amygdalus Dulcis (Sweet Almond) Seed Meal in 1983; at that time, this ingredient was named "Almond Meal." On the basis of the available animal data and limited clinical experience presented in the report, the Panel concluded this ingredient is safe for topical application to humans in the present practices of use and concentration (as described in that assessment). The Panel previously considered a re-review of this report and reaffirmed the 1983 conclusion, as published in 2005. Because it has been at least 15 years since the previous rereview was published, in accord with the Procedures, the Panel should consider whether the safety assessment of Prunus Amygdalus Dulcis (Sweet Almond) Seed Meal should be re-opened.

An extensive search of the world's literature was performed for studies dated 2001 forward. No relevant published data were found. A historical overview, comparison of original and new use data, and the search strategy used are enclosed with the report.

The frequency and concentration of use is presented both cumulatively by likely duration and exposure and individually by product category. Since the initial re-review was considered, the frequency of use has decreased slightly from 15 to 14 uses. In 2002, the maximum concentration of use for this ingredient was reported to be 27% in leave-on products and 2% in rinse-off products. No concentration of use was reported in the 2022 survey for this ingredient.

If upon review of the new studies and updated use data the Panel determines that a rereview is warranted, a Draft Amended Report will be presented at an upcoming meeting. If instead the Panel determines that the report should not be reopened, a draft rereview summary, conforming to the original conclusion, will be presented at an upcoming meeting.

Administrative Items - there are 5 rereview summaries (presented in 1 document) and administrative items.

1. Choleth-24 – RRsum – (Priya) – ***Dr. Belsito reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

2. HC Yellow No. 5 – RRsum – (Christina) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

3. Methyl Alcohol – RRsum – (Preethi) – ***Dr. Belsito reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

4. Peanut Glycerides – RRsum – (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

5. Phytantriol – RRsum – (Regina) – ***Dr. Belsito reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

6. Hair Dye Epidemiology Resource Document – Admin – (Jinqiu) – ***Dr. Cohen reports on day 2*** – Jinqiu has drafted a new iteration of the Hair Dye Epidemiology Resource Document for Panel review. The previous draft was reviewed by the Panel at the March 2021 meeting.

   At the March 2021 meeting, the Panel agreed on the inclusion of 12 additionally-identified studies, and maintained the conclusion that the available epidemiology data did not provide sufficient evidence for a causal relationship between personal hair dye use and cancer. In the current iteration, tables have been re-organized in light of the type of study (i.e., cohort, case-control, and meta-analysis), which cover more detailed information of each study, such as study population, diagnosis/publishing period, hair dye exposure patterns, ranking of the study (Rollison scale), adjudgment of confounder, as well as more risk ratio data, resulted from analysis and was stratified by race, gender, hair dye type, duration and frequency of use, etc. While it was not applicable to incorporate all data of the studies into the tables, particular attention was given to the relevant risk estimates associated with permanent dark dyes, long duration and high frequency of hair dye applications. For some studies, the authors have made specific clarifications on their findings (e.g., increased NHL risk was limited to women who used dark color or intense tone permanent hair dyes before 1980); such information was also noted in the tables for the Panel's consideration.

   The Panel requested continued monitoring of upcoming epidemiological data on the link between personal use of hair dyes and cancer risk. Since March 2021, six new epidemiological studies, including one meta-analysis study, one case-only study, one case-control study, and three prospective cohort studies, have been discovered. These additional studies are incorporated herein, and highlighted in yellow, for the Panel's consideration.

   The Panel should review this Document, especially noting the data presented in the new studies as well as the additional information incorporated in the reorganized tables. ***If this Document is in agreement with their thinking, it should be finalized and used to replace the version currently posted on the Findings & Resources Documents page https://www.cir-safety.org/cir-findings. If the Document is not considered ready for finalization, specific needs/edits therein should be made evident.***

7. Draft 2024 Priorities – Admin (Bart) – ***Dr. Belsito reports on day 2*** – The draft priority list 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.

   While this list includes only the lead ingredients, groupings of ingredients drafted by CIR Staff can be found in later pages of the document. The Panel is asked to consider these groupings. There are 20 reports proposed, covering 40 ingredients, on the 2024 Draft Priorities List. Once a proposal of a hair dye for assessment has been received from the PCPC Hair Color Technical Committee (HCTC), 21 new reports in total will be proposed for the 2024 docket. Reports previously prioritized and on the CIR docket at the end of 2023, as well as an extensive number of re-reviews of previous assessments, will supplement the total number of reports to be assessed in 2024. ***This Panel is asked to consider this draft priorities list and proposed groupings.***

Full Panel Meeting

The Panel will consider the 7 reports to be issued as final safety assessments, followed by the remaining reports advancing in the process (including the Tentative Report and Draft Reports). In addition, a consensus should be reached for the 6 rereview documents, the 5 rereview summaries, and the 2 administrative items.

Please remember, the meeting starts at 8:30 am on day 1 and day 2. It is likely that the full Panel session will conclude before lunch on day 2.

Looking forward to seeing you all ***virtually***!

Agenda
164th Meeting of the Expert Panel for Cosmetic Ingredient Safety
March 6th – 7th, 2023

Virtual via Microsoft Teams

Monday, March 6, 2023

8:30 AM	**WELCOME TO THE 164th EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:45 AM	**PRESENTATION – Modernization of Cosmetics Regulation Act (MoCRA)**	**Karin Ross/Tom Myers, PCPC**
9:45 AM	**TEAM MEETINGS**	**Drs. Cohen/Belsito**

Dr. Belsito's Team*

Admin (JZ)	Hair Dye Epi
FAR (CB)	Clays
FR (CB)	Basic Yellow 87
DAR (CB)	5-Amino-4-Chloro-*o*-Cresol
DAR (CB)	5-Amino-6-Chloro-*o*-Cresol
DAR (CB)	Basic Blue 99
RR (CB)	Sweet Almond
FR (RT)	*Rosa centifolia*
FAR (RT)	Octyldodecyl Stearoyl Stearate
RR (RT)	MIBK
RRsum (MF|BH)	RR Summaries (all)
Admin (BH|MF)	Priorities
FR (PC)	Trisodium Ethylenediamine Disuccinate
DR (PC)	Hyaluronates
RR (PC)	Stearalkonium Chloride
RR (PC)	Propylene Carbonate
FR (PR)	Mallow
FR (PR)	Polyhydroxystearic Acid
TR (PR)	Phenyl-Substituted Methicones
RR (PR)	Wild Yam
RR (PR)	Polyamino Sugar Condensate

Dr. Cohen's Team

FR (PC)	Trisodium Ethylenediamine Disuccinate
DR (PC)	Hyaluronates
RR (PC)	Stearalkonium Chloride
RR (PC)	Propylene Carbonate
RRsum (MF|BH)	RR Summaries (all)
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FR (PR)	Mallow
FR (PR)	Polyhydroxystearic Acid
TR (PR)	Phenyl-Substituted Methicones
RR (PR)	Wild Yam
RR (PR)	Polyamino Sugar Condensate
Admin (JZ)	Hair Dye Epi
FAR (CB)	Clays
FR (CB)	Basic Yellow 87
DAR (CB)	5-Amino-4-Chloro-*o*-Cresol
DAR (CB)	5-Amino-6-Chloro-*o*-Cresol
DAR (CB)	Basic Blue 99
RR (CB)	Sweet Almond
FR (RT)	*Rosa centifolia*
FAR (RT)	Octyldodecyl Stearoyl Stearate
RR (RT)	MIBK

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 || SM: Strategy Memo || Admin: Administrative item

BH: Bart Heldreth || MF: Monice Fiume || CB: Christina Burnett || PC: Priya Cherian || PR: Preethi Raj || RT: Regina Tucker || JZ: Jinqiu Zhu

*Team moves to breakout room. (For a virtual meeting, this means a separate Microsoft Teams meeting)

Tuesday, March 7, 2023			
8:30 AM	**WELCOME TO THE 164th FULL EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:40 AM	Admin	**MINUTES OF THE DECEMBER 2022 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 AM	**DIRECTOR'S REPORT**		**Dr. Heldreth**
9:10 AM	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**		
	Final Reports		
	FR (PC)	Trisodium Ethylenediamine Disuccinate **– *Dr. Belsito reports***	
	FR (RT)	*Rosa centifolia* – ***Dr. Cohen reports***	
	FAR (RT)	Octyldodecyl Stearoyl Stearate – ***Dr. Belsito reports***	
	FR (PR)	Mallow - *Malva sylvestris*-derived ingredients – ***Dr. Cohen reports***	
	FR (PR)	Polyhydroxystearic Acid – ***Dr. Belsito reports***	
	FR (CB)	Basic Yellow 87 – ***Dr. Cohen reports***	
	FAR (CB)	Clays - ***Dr. Belsito reports***	
	Reports Advancing		
	DAR (CB)	5-Amino-4-Chloro-*o*-Cresol – ***Dr. Cohen reports***	
	DAR (CB)	5-Amino-6-Chloro-*o*-Cresol – ***Dr. Belsito reports***	
	DAR CB)	Basic Blue 99 – ***Dr. Cohen reports***	
	DR (PC)	Hyaluronates – ***Dr. Belsito reports***	
	TR (PR)	Phenyl-Substituted Methicones – ***Dr. Cohen reports***	
	Other Items		
	RR (PR)	Wild Yam - Dioscorea Villosa (Wild Yam) Root Extract – ***Dr. Belsito reports***	
	RR (PR)	Polyamino Sugar Condensate – ***Dr. Cohen reports***	
	RR (RT)	MIBK – ***Dr. Belsito reports***	
	RR (PC)	Stearalkonium Chloride – ***Dr. Cohen reports***	
	RR (PC)	Propylene Carbonate – ***Dr. Belsito reports***	
	RR (CB)	Sweet Almond - Prunus Amygdalus Dulcis (Sweet Almond) Seed Meal – ***Dr. Cohen reports***	
	RRsum (PC|BH|MF)	Choleth-24 – ***Dr. Belsito reports***	
	RRsum (CB|BH|MF)	HC Yellow No. 5– ***Dr. Cohen reports***	
	RRsum (PR|BH|MF)	Methyl Alcohol – ***Dr. Belsito reports***	
	RRsum (PR|BH|MF)	Peanut Glycerides– ***Dr. Cohen reports***	
	RRsum (RT|BH|MF)	Phytantriol – ***Dr. Belsito reports***	
	Admin (JZ)	Hair Dye Epidemiology Resource Document – ***Dr. Cohen reports***	
	Admin (BH)	Priorities (Draft) – ***Dr. Belsito reports***	

ADJOURN – *The next will be held in-person on **June 12-13, 2023** at the Melrose Hotel, 2430 Pennsylvania Avenue, NW, Washington, DC. Please check the CIR website for details as the meeting approaches.*

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 || SM: Strategy Memo || Admin: Administrative item

BH: Bart Heldreth || MF: Monice Fiume || CB: Christina Burnett || PC: Priya Cherian || PR: Preethi Raj || RT: Regina Tucker || JZ: Jinqiu Zhu

ONE HUNDRED SIXTY-THIRD MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

December 5-6, 2022

The Hotel Melrose of Georgetown
2430 Pennsylvania Ave 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

Thomas Gremillion, J.D.

Industry

Alex Kowcz, M.B.A.

Government

Prashiela Manga, Ph.D. and Jannavi Srinivasan, 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

Regina Tucker, MS –Scientific Analyst

Information Services
Kevin Stone Fries, MLS - Information Services Manager

Other Meeting Attendees

(in-person only unless otherwise noted)

Name	***Organization***
Don Bjerke	Procter & Gamble
Carol Eisenmann	Personal Care Products Council
Carsten Goebel (virtual)	Wella
Kimberly Norman	Personal Care Products Council
Pushpa Rao	Combe
Hong Xie	US FDA
Lei Xu	US FDA

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 163rd meeting of the Expert Panel for Cosmetic Ingredient Safety. Dr. Bergfeld welcomed, in-person, new Panel members, Dr. David Cohen, Dr. Susan Tilton, Dr. Allan Rettie, and Dr. David Ross and expressed her appreciation to them for joining the Panel and for getting up-to-speed so quickly.

Dr. Bergfeld also expressed her appreciation towards CIR staff, CIR directors, and the CIR Scientific and Support Committee for all their continuing efforts in ensuring the safety assessments are of the highest quality.

Dr. Bergfeld acknowledged the presentation on hair dyes by Dr. Carsten Goebel and noted that the Panel would review 24 documents, including 2 final reports, 1 tentative report, 7 draft reports, 7 abbreviated re-reviews, and 7 re-review summaries. Dr. Bergfeld noted that 5 of these reports are on botanical ingredients, which continue to challenge the Panel. The administrative items included continued discussion of the format for cosmetic use tables and discussion on the strategy on 1,2,4-Trihydroxybenzene, a hair dye.

APPROVAL OF MINUTES

The minutes of the September 26-27, 2022 (162nd) Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth noted that CIR and the Panel had an exciting and effective year in 2022. He noted the wonderful addition of Ms. Regina Tucker to the CIR Staff as a Scientific Analyst. In addition to rapidly climbing the steep learning curve of starting this position, Regina concurrently completed her master's degree in skin biology this year. Regina was not the only Scientific Analyst to get her master's degree this year; Ms. Priya Cherian completed her master's in clinical toxicology by year end. Furthermore, Dr. Jinqiu Zhu, CIR Staff Toxicologist, added "DCST" (licensure as a toxicologist in China) to his list of registrations, which already included American and European equivalents.

Following the retirement of 3 Panel members this year, 3 new experts joined this membership, comprising Drs. Ross, Tilton, and Rettie. Dr. Ross completed his undergraduate and graduate work (in pharmacy and pharmaceutical sciences) at the University of Aston, Birmingham, UK and at the Medical Research Council Toxicology Unit in the UK. He was a Royal Society Postdoctoral Fellow at the Karolinska Institute in Stockholm, Sweden, and a Research Associate at the University of California in Berkeley, California. Dr. Ross joined the School of Pharmacy at the University of Colorado as an Assistant Professor and proceeded through the ranks to Professor with tenure and serving as Director of Graduate Studies. He is currently the Associate Dean for Research and Graduate Studies at the Skaggs School of Pharmacy and Pharmaceutical Sciences, in Aurora, Colorado.

Dr. Tilton completed her undergraduate work (biology) at Duke University, Durham, North Carolina, and is a graduate of the Ole Miss School of Pharmacy (MS, Pharmacology) in Oxford, Mississippi, and of the Oregon State University, College of Agricultural Sciences (PhD, Toxicology) in Corvallis, Oregon. She did her postdoctoral fellowship at the Fred Hutchinson Cancer Research Center, Seattle, Washington. Before returning to academia, Dr. Tilton joined the Pacific Northwest National Laboratory in Richland, Washington as Computational Biology & Bioinformatics Senior Research Scientist. She then returned to her doctorate alma mater as an Assistant Professor, quickly rising up to tenure. In addition to her role as an Associate Professor of Environmental and Molecular Toxicology, Dr. Tilton is currently the Director of Academic Programs in the same college.

Dr. Rettie completed his undergraduate work with honors (Pharmacy) at Heriot-Watt University, Edinburgh, Scotland, and is a graduate (PhD, Pharmaceutical Sciences) of the University Newcastle-upon-Tyne, England. He then proceeded to the University of Washington in Seattle, first as Senior Research Fellow in the Department of Pharmacology and ultimately as a faculty member in the Department of Medicinal Chemistry, which he chaired from 2000 to 2014. All 3 of these new additions to the Panel have acclimated to the meeting process at an impressive rate.

Including the 2 reports finalized at this meeting, the Panel issued 19 Final Reports in 2022, covering 163 ingredients. Following the process of peer-review, 3 issues of the *International Journal of Toxicology* were published this year, covering 191 ingredients.

CIR Staff were also very fortunate to be invited to share the CIR process and demonstrate how to utilize the safety assessments of the Panel, and the following presentation were made:

"CIR and the Expert Panel for Cosmetic Ingredient Safety: Hair Dye Ingredients," Bart Heldreth, *Safety and Risk Assessment of Hair Dye Ingredients*, Korea Society of Toxicology (KSOT) Annual Meeting, November 7, 2022

"CIR and the Expert Panel for Cosmetic Ingredient Safety: Safety Assessment in the US," Bart Heldreth, *Science Behind the Cosmetics* (*CANIPEC*), October 27, 2022

"CIR and the Expert Panel for Cosmetic Ingredient Safety: Who, Why, and What's in it for You," Bart Heldreth, *2022 PCPC Science Conference*, October 26, 2022

"CIR and the Expert Panel for Cosmetic Ingredient Safety: Safety Assessment in the US," Bart Heldreth, *Cosmetic Ingredients Safety Assessment and Its Impact in LATAM* (*CASIC*), October 14, 2022

"CIR and the Expert Panel for Cosmetic Ingredient Safety: Safety Assessment in the US," Bart Heldreth, meeting with leaders of KCA and JCIA (Korean and Japanese associations, respectively), October 3, 2022

"The Cosmetic Ingredient Review: Process and Use," Bart Heldreth, *CASIC's 30th Plenary Meeting: The Cosmetic and Cleaning Industry: Its Role in the Regional and Global Future*, June 2, 2022

"The Cosmetic Ingredient Review: Process and Use," Bart Heldreth, *IMA-NA Conference: Federal Issues Impacting the Minerals Industry*, May 9-12, 2022

Dr. Heldreth also noted an invitation to speak at a safety conference (in conjunction with the Cosmetics Europe Annual Conference) in mid-2023.

Dr. Heldreth reiterated his gratitude to each and every one of the members, liaisons, and staff for making this Panel what it is. He also remarked how wonderful it was to finally see everyone in-person at this meeting.

FINAL SAFETY ASSESSMENTS

Fatty Ethers
The Panel issued a Final Report with the conclusion that the following 8 ingredients are safe as used in the present practices of use and concentration described in the safety assessment:

Cetyl Dimethylbutyl Ether
Dicaprylyl Ether
Dicetyl Ether*
Didecyl Ether*
Diisononyl Ether*
Dilauryl Ether*
Dimyristyl Ether*
Distearyl Ether

**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.*

Previously, the Panel noted data stating that Dicaprylyl Ether and Distearyl Ether, the ingredients with the highest reported frequencies of use, were tested at ≥ 99.1% purity. Additionally, negative developmental and reproductive toxicity (DART) data, as well as negative genotoxicity data, a lack of structural alerts (e.g., Cramer classifications), and data demonstrating lack of dermal absorption mitigated systemic toxicity concerns. Irritation and sensitization study data results further assured the Panel of the dermal safety of these ingredients.

***Zingiber officinale* (Ginger)-Derived Ingredients**
The Panel issued a Final Report with the conclusion that the following 8 *Zingiber officinale* (ginger)-derived ingredients are safe as used in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root*
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice*
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

The Panel also determined that there was insufficient data to issue a conclusion of safety for Zingiber Officinale (Ginger) Leaf Cell Extract. (There are currently no reported uses for this ingredient.) In order to come to a conclusion of safety for Zingiber Officinale (Ginger) Leaf Cell Extract, the Panel requested method of manufacturing, composition, and impurities data. If the composition of Zingiber Officinale (Ginger) Leaf Cell Extract notably differs from the root-derived ginger ingredients, systemic toxicity data (e.g., 28-day dermal toxicity, genotoxicity, DART, and carcinogenicity data) and dermal irritation/sensitization data would be required. The need for sensitization data for Zingiber Officinale (Ginger) Extract was mitigated as this ingredient is used at very low concentrations. In addition, the Panel previously noted that the available systemic and sensitization data are sufficient to conclude safety for Zingiber Officinale (Ginger) Water, as this ingredient, according to manufacturers, is reported to be prepared via the distillation of ginger roots. The Panel noted the presence of constituents which are possible sensitizers, though at levels below concern for these individual ingredients. Accordingly, because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers.

TENTATIVE SAFETY ASSESSMENTS

Basic Yellow 87
The Panel issued a Tentative Report for public comment with the conclusion that Basic Yellow 87 is safe as a hair dye ingredient in the present practices of use and concentration described in the safety assessment.

Basic Yellow 87 is reported to function as a semi-permanent and oxidative hair dye in hair coloring products. The Panel recognizes that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the 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 Basic Yellow 87 has been reported to be used in 4 non-coloring cosmetic products (non-coloring hair conditioner, shampoo, and other hair preparations). The Federal FD&C Act mandates that color additives must be approved by the US FDA for their intended use before they are used. Basic Yellow 87 is an unapproved color additive in cosmetics products, and thereby, such uses are not permitted. Accordingly, these non-hair dye product uses are not within the purview of this Panel.

The Panel noted that the available toxicokinetic studies show that Basic Yellow 87 absorbs slowly through the skin, is not genotoxic, and has low reported concentrations of use. The Panel considered these findings, coupled with the short exposure time as a rinse-off product, and determined that the data are sufficient to conclude that Basic Yellow 87 is safe as a hair dye ingredient in the present practices of use and concentration.

The Panel discussed the issue of incidental inhalation exposure resulting from this ingredient. Basic Yellow 87 is reported to be used in an aerosol hair color spray (concentration not reported). Inhalation toxicity data were not available on this ingredient. However, the Panel noted that in aerosol products, the majority of the droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the low concentrations at which the ingredient is used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

***Malva sylvestris* (Mallow)-Derived Ingredients**

The Panel issued a Tentative Report for public comment with the conclusion that the following 8 *Malva sylvestris* (mallow)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Malva Sylvestris (Mallow) Extract
Malva Sylvestris (Mallow) Flower
Malva Sylvestris (Mallow) Flower Extract
Malva Sylvestris (Mallow) Flower/Leaf Extract
Malva Sylvestris (Mallow) Flower/Leaf/Stem Extract
Malva Sylvestris (Mallow) Leaf Extract
Malva Sylvestris (Mallow) Leaf Powder
Malva Sylvestris (Mallow) Oil

The safety of these ingredients was supported by the data on confirmed food use, which mitigated systemic toxicity concerns, and negative findings in human dermal irritation and sensitization studies on the Malva Sylvestris (Mallow) Flower/Leaf/Stem Extract and Malva Sylvestris (Mallow) Flower Extract. The Panel noted the presence of constituents (e.g., cinnamal) which are possible sensitizers, though at levels below concern for these individual ingredients. Accordingly, because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers.

Octyldodecyl Stearoyl Stearate

The Panel issued a Tentative Amended Report for public comment with the conclusion that Octyldodecyl Stearoyl Stearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating. The Panel discussed data from a repeated insult patch test on a makeup base containing 21% Octyldodecyl Stearoyl Stearate in which the test material indicated no potential for dermal irritation or sensitization. They also noted data from the original assessment that indicated an eyeliner formulation containing 7.5% Octyldodecyl Stearoyl Stearate was moderately irritating to the eye. Accordingly, formulators should be aware of this potential and ensure that products containing this ingredient should be formulated to be non-irritating.

Phytosteryl Glutamates

The Panel issued a Tentative Report for public comment and concluded the available data are insufficient to make a determination of safety for the following 3 phytosteryl glutamates.

Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate
Phytosteryl/Behenyl/ Octyldodecyl/Isostearyl Lauroyl Glutamate
Phytosteryl/Octyldodecyl Lauroyl Glutamate

The Panel determined that the data needs from the original Insufficient Data Announcement from the June 2022 Panel Meeting remain unmet. In order to come to a conclusion of safety for these cosmetic ingredients, the following additional data are needed:

- Method of manufacturing
- Impurities
- 28-day dermal toxicity
    - If positive, other toxicological endpoints (e.g., DART, genotoxicity, carcinogenicity, etc.) may be needed
- Sensitization and irritation data at maximum reported use concentrations
- Ocular irritation, if available

INSUFFICIENT DATA ANNOUNCEMENTS

6-Amino-*m*-Cresol

The Panel issued an Insufficient Data Announcement (IDA) for 6-Amino-*m*-Cresol. The additional data needed to determine safety for this hair dye ingredient are:

- Method of manufacture
- *in vivo* genotoxicity studies

6-Amino-*o*-Cresol

The Panel issued an IDA for 6-Amino-*o*-Cresol. The additional data needed to determine safety for this hair dye ingredient are:

- Method of manufacture
- Composition and impurities

- Concentration of use
- Absorption, distribution, metabolism, and excretion (ADME) studies
    - If absorbed, DART studies, genotoxicity studies, and potentially other endpoints

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

The Panel issued an IDA for the following 23 *Olea europaea* (olive)-derived ingredients.

Hydrolyzed Olive Fruit
Hydrolyzed Olive Fruit Extract
Hydrolyzed Olive Leaf Extract
Olea Europaea (Olive) Bark Extract
Olea Europaea (Olive) Branch Extract
Olea Europaea (Olive) Bud Extract
Olea Europaea (Olive) Flower Extract
Olea Europaea (Olive) Flower Water
Olea Europaea (Olive) Fruit
Olea Europaea (Olive) Fruit Extract
Olea Europaea (Olive) Fruit Juice
Olea Europaea (Olive) Fruit Juice Extract
Olea Europaea (Olive) Fruit Unsaponifiables
Olea Europaea (Olive) Fruit Water
Olea Europaea (Olive) Husk Powder
Olea Europaea (Olive) Leaf
Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Seed
Olea Europaea (Olive) Seed Powder
Olea Europaea (Olive) Wood Extract

The additional data needed to determine safety for these cosmetic ingredients are:

- Method of manufacture for Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, Hydrolyzed Olive Leaf Extract, Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) Leaf, Olea Europaea (Olive) Sap Extract, Olea Europaea (Olive) Seed Powder, and Olea Europaea (Olive) Wood Extract
- Composition and impurities data for Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, Hydrolyzed Olive Leaf Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Flower Water, Olea Europaea (Olive) Fruit Unsaponifiables, Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) Leaf Water, and Olea Europaea (Olive) Seed Powder
- 28-day dermal toxicity data on Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) Sap Extract, Olea Europaea (Olive) Seed, Olea Europaea (Olive) Seed Powder, and Olea Europaea (Olive) Wood Extract
    - If positive, additional data (e.g., DART and genotoxicity data) may be needed
- Dermal irritation and sensitization data for Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, Hydrolyzed Olive Leaf Extract, Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Fruit Extract (at maximum use concentration), Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
- Ocular irritation data for Olea Europaea (Olive) Fruit Extract and Olea Europaea (Olive) Leaf Extract, if available

***Zanthoxylum piperitum*-Derived Ingredients**

The Panel issued an IDA for the following 4 *Zanthoxylum piperitum*-derived ingredients.

Zanthoxylum Piperitum Fruit Extract
Zanthoxylum Piperitum Oil
Zanthoxylum Piperitum Peel Extract
Zanthoxylum Piperitum Peel Water

The additional data needed to determine safety for these cosmetics ingredients are:

- Method of manufacture for Zanthoxylum Piperitum Fruit Extract and Zanthoxylum Peel Water
- Impurities data for Zanthoxylum Piperitum Peel Water
- Further concentration of use data, if available

RE-REVIEWS

In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued safety assessments approximately every 15 years. At this meeting, the Panel considered 6 previous assessments for re-review. The Panel determined that the following report should be reopened; a Draft Amended Report will be presented to the Panel for this safety assessment at a later meeting.

- Basic Blue 99 – 1 ingredient

In contrast, the Panel reaffirmed the conclusions reached for the following 5 safety assessments (choosing to not re-open the original reports). A re-review summary will be presented to the Panel for each of these safety assessments at an upcoming meeting.

- HC Yellow No. 5 – 1 ingredient
- Choleth-24 – 1 ingredient
- Methyl Alcohol – 1 ingredient
- Peanut Glycerides – 1 ingredient
- Phytantriol – 1 ingredient

RE-REVIEW SUMMARIES

Once the Panel determines to not reopen a previously-issued safety assessment, thereby reaffirming the existing conclusion, a rereview summary is prepared. The Panel approved the following 7 re-review summaries:

- Acid Orange 3 – 1 ingredient
- Sodium Lauryl Sulfoacetate – 1 ingredient
- Chloroxylenol – 1 ingredient
- Hexamidine – 1 ingredient
- Erythorbic Acid – 2 ingredients
- Glyceryl Diesters – 17 ingredients
- Mink Oil – 1 ingredient

Strategy Memo – Amend 2023 Priorities to include 1,2,4-Trihydroxybenzene (THB)

CIR was made aware of issues overseas with assessing the safety of 1,2,4-Trihydroxybenzene (sometimes referred to as THB), which is a hair dye ingredient. Interestingly, this ingredient is reported to be an "auto-oxidative" hair dye, not requiring hydrogen peroxide to develop. The EU SCCS has previously assessed this ingredient and concluded that it is not safe, based on concerns of potential genotoxicity when used as an "auto-oxidative" hair dye component in permanent hair dye formulations. As a result of the SCCS opinion, the European Commission has regulated this ingredient to Annex II – Prohibited Substances. Accordingly, the Panel was asked if they found it appropriate to amend their 2023 Priorities to include this ingredient; the Panel agreed.

Thus, the 2023 Priorities are now amended. There are now 18 reports proposed (2 of the "per FOU" ingredients below are proposed to be reviewed together in 1 report) on the 2023 Amended Final Priorities List. Reports previously prioritized and on the CIR docket at the end of 2022, as well as a significant number of re-reviews of previous assessments, will supplement the total number of reports to be assessed in 2023.

2023 Amended Final Priorities List

Ingredients	Frequency of Use (FOU) Data Year 2022
For cause	
HC Blue No. 15	**22**
1,2,4-Trihydroxybenzene	**23**
Isopropyl Cloprostenate & Ethyl Tafluprostamide	**"3"**
Per FOU	
Sodium Hydrosulfite	**246**
Pelargonium Graveolens Flower Oil	**236**
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	**234**
Diglycerin	**211**
Polyglycerin-3	**208**
Sigesbeckia Orientalis Extract	**202**
Houttuynia Cordata Extract	**201**
Malva Sylvestris (Mallow) Extract	**198**
Palmitoyl Pentapeptide-4	**198**
Salix Alba (Willow) Bark Extract	**197**
Centaurea Cyanus Flower Extract	**196**
Lactobacillus Ferment	**196**
Copper Gluconate	**192**
Inositol	**190**
Paeonia Suffruticosa Root Extract	**189**
Nelumbo Nucifera Flower Extract	**182**

Petition to Reopen Brown Algae

CIR received a petition, along with accompanying data, to reopen the safety assessment of brown algae ingredients. Specifically, data were provided in an effort to meet the insufficient data needs for Cladosiphon Novae-Caledoniae Extract, Ecklonia Maxima Extract, and Ecklonia Maxima Powder. While significant quantities of relevant safety data were provided, the Panel felt that the data were yet insufficient for all 3 of these ingredients, which originally received an insufficient data conclusion in the 2019 final report on brown algae ingredients. Notably, these data needs include dermal sensitization data for Cladosiphon Novae-Caledoniae Extract and further systemic toxicity data for Ecklonia Maxima Extract and Ecklonia Maxima Powder. Accordingly, the Panel denied this petition to reopen the Brown Algae report.

Use Table Format

The Panel reviewed further proposed changes to the Use Table format that is utilized in each report. Panel members stated that, at this time, it is clear further revisions should be made, resulting in a hybrid of the 2 presented formats. A revised hybrid format will be proposed at a future meeting.

Presentation – Hair Dye Ingredients

A thorough and insightful presentation on hair dye chemistry and toxicology was provided by Dr. Carsten Goebel, of Wella. The purpose of the presentation was to impart information on the relevant points related to assessing the safety of hair dye ingredients. This presentation, as well as an update to the hair dye allergy alert test, are now available on the meeting page (https://www.cir-safety.org/meeting/163rd-expert-panel-meeting).