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EXPERT PANEL MEETING
December 5-6, 2022

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: 163rd Meeting of the Expert Panel — Monday and Tuesday, December 5-6, 2022
Date: November 10, 2022

Welcome to the first in-person Panel Meeting since 2019! The agenda and accompanying materials for the 163rd Expert Panel Meeting, to be held on December 5-6, 2022, are now available. Please note that this meeting is on a ***Monday and Tuesday***. The location is ***new*** – this meeting will be held in-person at the Melrose Georgetown Hotel, 2430 Pennsylvania Avenue NW, Washington, DC 20037. We will be trying out a virtual component to this in-person meeting; however, this component will be only of a spectator nature, and will not allow for any interaction with the Panel or Staff. If you are unable to attend in-person and are interested in seeing the proceedings of the Panel, you may register to watch virtually, in advance of the meeting, at the meeting page:

https://www.cir-safety.org/meeting/163rd-expert-panel-meeting

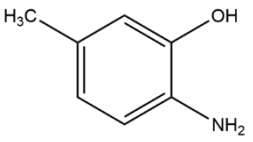
The meeting agenda includes the consideration of 10 reports advancing in the review process, including 2 final reports, 1 tentative report, and 7 draft reports. Also on the agenda are 14 rereview documents (7 proposals for rereview and 7 rereview summaries). ***In each case of a rereview proposal, the 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 is 1 strategy memo. Please note that Monice has included both old and new use tables, for your comparison, in 4 of the draft reports.

In addition, the team meetings on Day 1 will kick-off with a speaker (Dr. Carsten Goebel) on the topics of hair dye chemistry and toxicology. With 7 hair dye related items on the agenda, this presentation should prove to be quite timely.

Team Meetings

Draft Report - There are 7 draft reports for review. - Sufficient data to proceed, or issue an IDA?

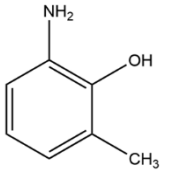
1. 6-Amino-*m*-Cresol – DAR (Christina) – ***Dr. Cohen reports on day 2*** - The Panel previously reviewed the safety of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol in an assessment that was published in 2004. In June 2022, the Panel re-opened the safety assessment for these ingredients, due to some of these hair dyes being banned for use in cosmetics by the European Commission. Because the Panel determined that data for these amino cresol hair dye ingredients could not be read-across, rather than including all 6 ingredients in one amended report, re-reviews of each hair dye will now be presented as individual stand-alone reports. In the original report, the Panel concluded that 6-Amino-*m*-Cresol is safe as used in oxidative and non-oxidative (semi-permanent) hair dyes.



   According to 2022 VCRP survey data, 6-Amino-*m*-Cresol has 2 reported uses in hair dyes and colors. The results of the concentration of use survey provided by the Council in 2022 report that this ingredient is used at 0.69% in hair dyes and colors. Compared with the historical data, the frequency of use has remained the same, but the concentration of use has decreased. When the original safety assessment was published in 2004, 6-Amino-*m*-Cresol was reported to have 2 uses in hair dye and color formulations, according to 1998 VCRP data. At that time, 6-Amino-*m*-Cresol was reported to be used at 2.4% in hair dyes and colors, according to a survey performed by industry.

   Since the June 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 Insufficient Data Announcement (IDA).

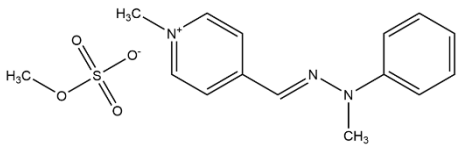
2. 6-Amino-*o*-Cresol – DAR (Christina) – ***Dr. Belsito reports on day 2*** – The Panel previously reviewed the safety of 6-Amino-*o*-Cresol (along with 6-Amino-*m*-Cresol above) in an assessment that was published in 2004. In June 2022, the Panel determined to reassess the safety of this ingredient. In the original report, the Panel concluded that 6-Amino-*o*-Cresol is safe for use in oxidative hair dyes, but the data are insufficient to support safety in non-oxidative (semi-permanent) hair dyes.



   According to 2022 VCRP survey data, 6-Amino-*o*-Cresol has no reported uses. The results of the concentration of use survey provided by the Council in 2022 also report no uses for this ingredient. When the original safety assessment was published in 2004, 6-Amino-*o*-Cresol was reported to have no uses (data acquired from the FDA in 1998). At that time, 6-Amino-*o*-Cresol was reported to be used at 0.7% in hair dyes and colors, according to a survey performed by industry.

   Since the June 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.

3. Basic Yellow 87 – DR (Christina) – ***Dr. Belsito reports on day 2*** - This is the first time the Panel is reviewing this ingredient. The Scientific Literature Review (SLR) of Basic Yellow 87 was issued by CIR on July 25, 2022. This ingredient is reported to function in cosmetics as a hair colorant.



   According to 2022 VCRP survey data, Basic Yellow 87 is used in a total of 40 formulations. Of these reported uses, the majority (36) are in rinse-off hair coloring products. Four reported uses were in non-coloring hair products. One use in an aerosol hair color spray was also reported. The results of the concentration of use survey provided by the Council in 2022 indicate that Basic Yellow 87 is used at up to 1% in hair dyes and colors and up to 0.02% in coloring shampoos.

At the September 2022 Panel meeting, a change to the current Use Table format was discussed. At that time, the Panel requested that both Use Table formats (i.e., the existing and the proposed format) be included in a Draft Report to provide a side-by-side comparison. That has been presented in this document to provide an example for a hair dye ingredient that has reported non-hair coloring uses. ***CIR is asking that you compare the tables and provide your preference as to which format should be used in all future safety assessments.***

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

4. Mallow - *Malva sylvestris* – DR (Preethi) – ***Dr. Belsito reports on day 2*** – This is the first time the Panel is seeing a safety assessment of these 8 *Malva sylvestris*-derived cosmetic ingredients.

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

Due to a dearth of published data found upon search of these ingredients, a Scientific Literature Review Notice to Proceed (SLR NTP) was announced on September 14, 2022. Information was sought in a wide range of areas, especially chemistry (including method of manufacture, composition, and impurities); toxicity (especially dermal); developmental and reproductive toxicity; genotoxicity; carcinogenicity; and dermal irritation/sensitization data.

In response, data with regard to methods of manufacture, composition, a human repeat insult patch test (product containing 0.0125% Malva Sylvestris (Mallow) Flower/Leaf/Stem Extract) and various specifications were received.

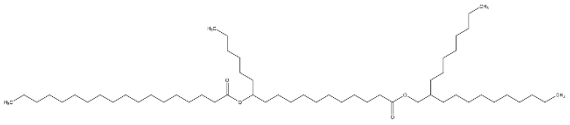
According to 2022 VCRP survey data, all the ingredients named in this assessment are reported to be in use. Malva Sylvestris (Mallow) Extract is reported to be used in 198 formulations, 184 of which are leave-on products, and Malva Sylvestris (Mallow) Flower Extract is reported to be used in 72 formulations. The other ingredients have 5 or fewer reported uses. The results of the concentration of use survey conducted by the Council in 2022 indicate Malva Sylvestris (Mallow) Flower Extract has the highest reported maximum concentration of use (at 0.1% in non-spray body and hand products, and depilatories).

Although frequency of use data were reported by the VCRP for all ingredients, concentration of use data were only received for Malva Sylvestris (Mallow) Extract and Malva Sylvestris (Mallow) Flower Extract.
Malva Sylvestris (Mallow) Extract is reported to be used in products that can result in incidental ingestion, such as 52 lipstick formulations (concentration of use not provided). Malva Sylvestris (Mallow) Extract and Malva Sylvestris (Mallow) Flower Extract are reported to be used in products applied near the eye, in 6 and 2 other eye makeup preparations, respectively (concentrations of use not provided). Of note, Malva Sylvestris (Mallow) Flower Extract has reported uses in baby shampoo, lotions, oils, powders, and creams (2 reported uses; concentrations of use not provided).

Furthermore, some of the *Malva sylvestris* (mallow)-derived ingredients are used in powder formulations, and could possibly be inhaled. For example, Malva Sylvestris (Mallow) Extract and Malva Sylvestris (Mallow) Flower Extract are reported to be used in 2 and 5 face powder formulations, respectively (concentrations of use not provided).

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.

5. Octyldodecyl Stearoyl Stearate – DAR (Regina) – 
Dr. Belsito reports on day 2 – In its initial assessment of Octyldodecyl Stearoyl Stearate, the Panel found that the data were insufficient to determine safety, and a Final Report with such conclusion was published in 2001. Subsequently, the Panel's data needs were met, and a Final Amended Report with the following conclusion was published in 2005: Octyldodecyl Stearoyl Stearate is safe for use in cosmetic products in the practices of use and concentration described in this safety assessment. In September 2022, the Panel re-opened the safety assessment of this ingredient. In its decision to reopen the assessment, the Panel cited updated usage data and significant increases in concentration of use.

The reported frequency of use of this ingredient has increased since it was last reviewed. According to 2022 VCRP data, the ingredient is reported to be used in 605 formulations; according to the 2005 Amended Report, the reported frequency of use was 106 (2001 VCRP data). Of note, the frequency of use for formulations resulting in incidental ingestion and mucous membrane contact (lipsticks) increased from 1 to 48 uses, and use in products applied near the eye area increased from 35 uses in 2001 to 322 uses in 2022. Additionally, concentrations of use have increased since the last review. The highest reported use concentration in 2022 is in lipstick (28%); in 2001, the maximum concentration of use reported for lipsticks was 10%. Use concentrations in the eye area also increased; the maximum concentration reported in eye shadow was 10% in 2001, and is now 18.5% in 2022.

At the September 2022 Panel meeting, a change to the current Use Table format was discussed. At that time, the Panel requested that both Use Table formats (i.e., the existing and the proposed format) be included in a Draft Report to provide a side-by-side comparison. That has been presented in this document to impart an example for an amended report, which has current and historical use values. It should be noted that while most of the descriptors in the body of the report highlighting the types of use of the ingredients (i.e., eye area, mucous membrane, inhalation, etc.) will remain if the new format is adopted, reference to the highest leave-on/rinse-off concentrations of use will not be included, in that it is not definitively known what the duration of exposure is for all formulations. (This is one of the driving issues behind the consideration of a new Use Table format.) ***The CIR staff requests that you compare the tables and provide your preference as to which format should be used in all future safety assessments.***

Since the September meeting, unpublished data were received, including a use study summary (lip balms containing 28% Octyldodecyl Stearoyl Stearate) and a repeated insult patch test (makeup base containing 21.0112% Octyldodecyl Stearoyl Stearate).

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.

6. Olive - *Olea europaea* – DR (Christina) – 
Dr. Cohen reports on day 2 – The SLR of these 20 ingredients was issued by CIR on July 25, 2022. Most of the *Olea europaea* (olive)-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin-conditioning agents (emollient, humectant, or miscellaneous). Olea Europaea (Olive) Husk Powder and Olea Europaea (Olive) Seed Powder are reported to only function as abrasives.

According to 2022 VCRP survey data, Olea Europaea (Olive) Leaf Extract has the highest frequency of use; it is reported to be used in 182 formulations, with a majority of uses in leave-on skin care preparations. Olea Europaea (Olive) Fruit Extract is reported to be used in 118 formulations, also with the majority of uses in leave-on skin care preparations. All other in-use ingredients are reported to be used at much lower numbers. The results of the concentration of use survey conducted by the Council in 2020 indicate that Olea Europaea (Olive) Leaf Extract has the highest concentration of use in a leave-on formulation; it is used at up to 2% in suntan preparations. The highest concentration of use reported for products resulting in rinse-off dermal exposure is 10% in Olea Europaea (Olive) Fruit

Unsaponifiables in shaving cream. Eleven ingredients are reported to be not in use, according to the VCRP and industry survey.

At the September 2022 Panel meeting, a change to the current Use Table format was discussed. At that time, the Panel requested that both Use Table formats (i.e., the existing and the proposed format) be included in a Draft Report to provide a side-by-side comparison. That has been presented in this document to impart an example of the different formats in a report with numerous ingredients. It should be noted that while most of the descriptors in the body of the report highlighting the types of use of the ingredients (i.e., inhalation, mucous membrane, etc.) will remain if the new format is adopted, reference to the highest leave-on/rinse-off concentrations of use will not be included, in that it is not definitively known what the duration of exposure is for all formulations. (This is one of the driving issues behind the consideration of a new Use Table format.) ***The CIR staff requests the Panel to compare the tables and provide their preference as to which format should be used in all future safety assessments.***

In addition to concentration of use survey data, the Council provided data regarding method of manufacture, chemical properties, composition, irritation, sensitization, and photosensitization data. The Panel should note that information from one supplier states that the product they sell under the INCI name Olea Europaea (Olive) Fruit Extract is actually olive oil. The ingredient names for olive fruit extract and olive oil cover similar materials and may in some cases be synonymous. As a reminder, the Panel has previously reviewed the safety of Olea Europaea (Olive) Fruit Oil and concluded that this ingredient is safe for use in cosmetics.

Of note for Panel consideration, the Council has asked if Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, and Hydrolyzed Olive Leaf Extract should be included in this safety assessment. Currently, no uses are reported in the VCRP for these ingredients. The safety assessment does include data on hydrolyzed olive fruit extract that the Panel may or may not consider relevant to assessing the safety of the ingredients currently listed in the report. ***Does the Panel want to add these 3 ingredients to the safety assessment?***

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

7. <u>*Zanthoxylum piperitum*</u>– DR (Regina) – ***Dr. Cohen reports on day 2*** – This is the first time the Panel is reviewing these 4 *Zanthoxylum piperitum*-derived ingredients. The SLR was announced on August 3, 2022.

According to 2022 VCRP data, Zanthoxylum Piperitum Fruit Extract is reported to be used in 180 cosmetic products. Although this ingredient has the highest reported frequency of use for the ingredients in this group, and it is used in numerous product categories, the results of a concentration of use survey provided by the Council in 2021 only report concentration of use data for Zanthoxylum Piperitum Fruit Extract in one product category; according to the survey, it is used at a maximum use concentration up to 0.01% in spray body and hand products. Zanthoxylum Piperitum Peel Extract is the only other ingredient in this report that is reported to be in use; it is reported to be used in 12 formulations at maximum use concentrations up to 0.0022%. According to VCRP and Council survey data, 2 of the 4 ingredients, i.e., Zanthoxylum Piperitum Oil and Zanthoxylum Piperitum Peel Water, are not currently in use in cosmetic products.

Cosmetic products containing *Zanthoxylum piperitum*-derived ingredients may incidentally come in contact with the eyes or mucous membranes (concentration data for these formulation-types not provided). It should be noted that Zanthoxylum Piperitum Fruit Extract is reported to be used in 1 baby product (use concentration not provided). Additionally, some of the ingredients are used in cosmetic sprays and powders, and could be incidentally inhaled; for example, Zanthoxylum Piperitum Fruit Extract and Zanthoxylum Piperitum Peel Extract are reported to be used in products that are known to be sprayed (up to 0.01% in body and hand products and up to 0.0000018% in night products, respectively), and Zanthoxylum Piperitum Peel Extract is reported to be used in face powders at a maximum use concentration of 0.0000022%.

Since the issuing of the SLR, unpublished data were received with regard to method of manufacture and composition. Some of this unpublished data were submitted for Zanthoxylum Piperitum Seed Oil; however, this ingredient is not currently included in the report.

It should be noted that Zanthoxylum Piperitum Seed Oil has no reported uses in the VCRP, and it is not known at what concentrations it is used at (if in use) because it was not included in the concentration of use survey. Additionally, according to the *Dictionary*, Zanthoxylum Piperitum Seed Oil is reported to function in cosmetics as a fragrance ingredient and flavoring agent; fragrance ingredients are typically left to the purview of the RIFM. Also of note is the fact that this ingredient is derived from the seed, while the 4 ingredients currently named in this report are derived from the fruit or the peel. (The seed oil is a volatile oil with likely a very different composition from the ingredients named in this report.) ***Therefore, the CIR staff requests Panel input on whether Zanthoxylum Piperitum Seed Oil should be included in this report.*** If it is determined that this ingredient should be added, it, and the data submitted, will be added to the report following the meeting. If this ingredient is not added to the report, are these data relevant?

At the September 2022 Panel meeting, a change to the current Use Table format was discussed. At that time, the Panel requested that both Use Table formats (i.e., the existing and the proposed format) be included in a Draft Report to provide a side-by-side comparison. That is presented in this report for your review. It should be noted that while most of the descriptors in the body of the report highlighting the types of use of the ingredients (i.e., inhalation, mucous membrane, etc.) will remain if the new format is adopted, reference to the highest leave-on/rinse-off concentrations of use will not be included, in that it is not definitively known what the duration of exposure is for all formulations. (This is one of the driving issues behind the consideration of a new Use Table format.) ***The CIR staff requests the Panel to compare the tables and provide their preference as to which format should be used in all future safety assessments.***

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. Phytosteryl Glutamate – TR (Regina) – ***Dr. Cohen reports on day 2*** – After reviewing the Draft Report at the June 2022 meeting, an IDA on these 3 Phytosteryl Glutamate ingredients was issued by the Panel with the following data needs:

- Method of manufacturing
- Impurities data
- 28-day dermal toxicity
    - If positive, other toxicological endpoints, including developmental and reproductive toxicity, genotoxicity, and carcinogenicity data, may be needed
- Irritation and sensitization data for Phytosteryl/Octyldodecyl Lauroyl Glutamate at maximum concentration of use
- Ocular irritation data, if available

The following data were received and have been incorporated into the current iteration of the report: a reverse mutation assay, an *in vitro* chromosome aberration assay, a 28-day oral toxicity (gavage) study, a direct peptide reactivity assay data, human cumulative irritation patch tests, a human repeated insult patch test, an EpiOcular™ assay, and summary information.

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.

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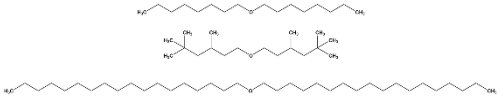
Draft Final Reports - There are 2 Draft Final Reports for consideration. - Review these drafts, especially the rationales provided in the Discussion sections, and issue these as Final Reports, as appropriate.

1. Fatty Ethers – FR (Preethi) – ***Dr. Cohen reports on day 2*** – At the June 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that these 8 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.



   Since the issuance of the Tentative Report, CIR has received no new unpublished data. Comments on the Tentative Report have been received and addressed. After carefully reviewing the Abstract, Discussion, and Conclusion, the Panel should be prepared to issue a Final Report.

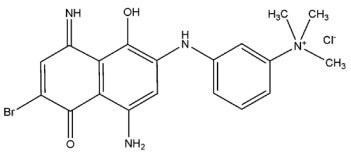
2. Ginger - *Zingiber officinale* – FR (Priya) – ***Dr. Belsito reports on day 2*** – At the June 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that the 7 *Zingiber officinale* (ginger) root- and rhizome-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing. In addition, the Panel concluded that the available data are insufficient data to make a determination of safety for Zingiber Officinale (Ginger) Extract and Zingiber Officinale (Ginger) Leaf Cell Extract under the intended conditions of use in cosmetic formulations.

   In order to determine safety for Zingiber Officinale (Ginger) Leaf Cell Extract, the Panel requires 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-d dermal toxicity, genotoxicity, developmental/reproductive toxicity, and carcinogenicity data) would also be required. Insufficiencies for Zingiber Officinale (Ginger) Extract are irritation and sensitization data at the maximum use concentration.

   No additional data were submitted. 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.

Abbreviated Rereviews (i.e., rereview proposals) – There are 7 rereview documents – In each case, the Panel is only being asked if the report should be reopened.

1. Basic Blue 99 – RR (Christina) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Basic Blue 99 in 2007 with the conclusion that this ingredient is safe as a hair dye ingredient in the present practices of use and concentration. Because it has been at least 15 years since it was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of Basic Blue 99 should be re-opened.



   An exhaustive search of the world's literature was performed for studies dated 2003 forward. A historical overview, comparison of original and new use data, and the search strategy used are enclosed herein. New case studies reporting allergic reactions to Basic Blue 99, the analysis of Basic Blue 99 by a new predictive dermal irritation assay, and additional chemical properties data were discovered. There are no restrictions for use of Basic Blue 99 in the European Union; however, the European Commission's Scientific Committee on Consumer Safety (SCCS) determined that they could not evaluate the safety of Basic Blue 99 due to the variability of the ingredient's composition.

   Since this report was first considered, the frequency of use has decreased from 51 to 38 uses; however, non-hair dye uses have been reported in the 2022 VCRP data, including 1 use in nail polish and enamel and 6 uses in non-coloring hair products. In 2002, the maximum concentration of use for hair coloring products was reported to be 2%. A survey performed by the Council in 2022 indicated this ingredient is currently used in hair dyes at no greater than 0.2%.

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. Brown Algae – RR (Priya) – ***Dr. Belsito reports on day 2*** – At the September 2019 meeting, the safety assessment of brown algae-derived ingredients as used in cosmetics was finalized, with the conclusion that 68 of the 82 brown algae-derived ingredients were safe in cosmetics in the present practices of use and concentration as described in that assessment. The remaining 14 ingredients, including Cladosiphon Novae-Caledoniae Extract, Ecklonia Maxima Extract, and Ecklonia Maxima Powder, were found to have insufficient data to support a conclusion of safety. The insufficiencies for these 3 ingredients include systemic toxicity data (GRAS status or oral exposure data) and dermal sensitization data.

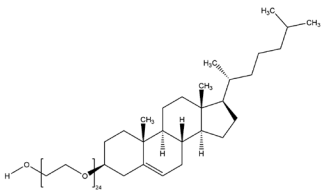
Since the issuing of the final report, unpublished data have been received via the Council on Cladosiphon Novae-Caledoniae Extract and as a direct submission to CIR on 2 trade name formulations containing Ecklonia Maxima Extract. These data include physical and chemical properties, manufacturing, composition, impurities, acute toxicity, genotoxicity, dermal irritation/sensitization, photosensitization, phototoxicity, ocular irritation data, and adverse event reports.

In addition to the unpublished data, a report on the anti-melanogenic and photo-protective effects of a phlorotannin-enriched *Ecklonia maxima* extract was found in the literature. The extract resulted in a statistically-significant inhibition of tyrosinase activity and melanogenesis in alpha-melanocyte-stimulating hormone-stimulated B16F10 cells. The extract also resulted in an increase in viability and a decrease in intracellular reactive oxygen species levels in UVB-induced HaCaT cells. In addition, a study reported the use of *Ecklonia maxima* in nutritional supplements and animal feed.

According to 2019 FDA VCRP data, there were no reported uses for Cladosiphon Novae-Caledoniae Extract; however, 3 uses are now reported (2022 VCRP) for Cladosiphon Novae-Caledoniae Extract (2 body and hand formulations and 1 skin freshener formulation). Ecklonia Maxima Extract and Ecklonia Maxima Powder also had no reported uses in 2019, and do not have any reported in 2022 either.

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.

3. Choleth-24 – RR (Priya) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Choleth-24 in 1982, with the conclusion that this ingredient is safe for topical applications to humans in the present practices of use and concentration, as stated in that report. The Panel previously considered a re-review of this report and determined to not reopen the assessment, as published; thus, the conclusion published in 2005 was a reaffirmation of the original.



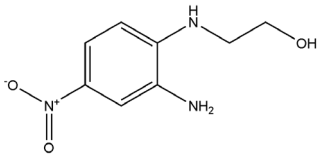
Because it has been 15 years since the previous re-review was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of Choleth-24 should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1998 forward. No new toxicological studies were found in the literature; however, it should be noted that Choleth-24 is an inactive ingredient in two FDA-approved drug formulations. In addition, Choleth-24 is not restricted for use in cosmetics according to the European Union CosIng database.

According to the original (1982) safety assessment, "choleth is the ethoxylated cholesterol fraction of lanolin alcohol. Since lanolin alcohol may contain as much as 38% cholesterol, ethoxylating these alcohols to produce laneths also produces choleths." It should be noted that some sterol-containing PEG ethers (e.g., Laneth 25) contain choleths, and have been reviewed by the Panel. These ethers were last reviewed as part of the safety assessment of alkyl PEG ethers, for which the Panel concluded safe in the present practices of use and concentration as stated in that assessment when formulated to be non-irritating. (Additionally, the 1982 safety assessment of Choleth-24 included data from the 1982 assessment of laneths.)

The frequency of use for Choleth-24 has decreased from 191 uses reported in 2002 to 33 uses reported in 2022. In 2002, Choleth-24 was reported to be used at up to 1.3%. No uses were reported for Choleth-24 in a 2022 concentration of use survey performed by the Council.

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. HC Yellow No. 5 – RR (Christina) – ***Dr. Belsito reports on day 2*** – The Panel first published a review of the safety of HC Yellow No. 5 in 2007, with the conclusion that this ingredient is safe as a hair dye ingredient in the present practices of use and concentration described in the safety assessment.

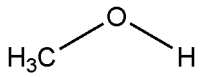


Because it has been at least 15 years since it was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of HC Yellow No. 5 should be re-opened. An exhaustive search of the world's literature was performed for studies dated 2003 forward. No relevant published data were found. At the time the original report was written, there were no restrictions on the use of HC Yellow No. 5 in cosmetics in Europe; however, European regulations regarding cosmetic ingredients now categorize HC Yellow No. 5 in Annex II, the list of substances prohibited in cosmetic products in Europe. This is likely due to the determination by the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) that there were inadequate data to issue a safety dossier, which was reported in the original CIR safety assessment.

Since this report was first considered, the frequency of use has decreased from 37 to 5 uses; however, non-hair dye uses have been reported in the 2022 VCRP data, including 2 uses in nail polish and enamel and 1 use in body and hand skin care products. In 2003, the maximum concentration reported for use in hair coloring formulations was reported to be 1.6%. A survey performed by the Council in 2022 had no reported concentrations of use.

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. Methyl Alcohol – RR (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Methyl Alcohol in 2001, with the conclusion that Methyl Alcohol is safe as used to denature alcohol used in cosmetic products.



Because it has been at least 15 years since the final report was published, in accordance with CIR Procedures, the Panel should consider whether the safety assessment of Methyl Alcohol should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1996 forward. Most of the toxicological and dermal irritation and sensitization data that were found therein are from a European Chemicals Agency (ECHA) dossier and a Screening Information Dataset (SIDS) Initial Assessment Report on Methyl Alcohol. Of note, subchronic oral and chronic inhalation studies in rats, mice, and monkeys, as well as long-term exposure (18 months up to a lifetime) carcinogenicity studies in mice and rats were found. Additionally, a guinea pig maximization test exhibiting weak, but negligible, sensitizing potential (50% Methyl Alcohol during induction and 100% during challenge) were found.

The number of reported uses has remained constant since the 2001 review. In 2022, FDA VCRP data indicate that Methyl Alcohol has 3 reported uses, while 4 uses were reported in 2001. The maximum use concentration for this ingredient appears to have decreased. Because concentration of use data were not reported to the FDA at the time of the 2001 report, 1984 data were used, which indicated that the reported concentration of use was 0.1 - 5%. In 2022, the maximum reported concentration of use is 0.15% in hair dyes and colors.

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.

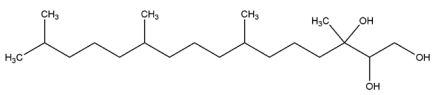
6. Peanut Glycerides – RR (Preethi) – ***Dr. Belsito reports on day 2*** – The Panel first published a review of the safety of Peanut Glycerides, as part of a larger group of ingredients, in 2001, with the conclusion that Peanut (Arachis Hypogaea) Oil, Hydrogenated Peanut Oil, Peanut Acid, and Peanut Glycerides are safe as used in cosmetic products as described in the safety assessment, and that the available data were insufficient to support the safety of Peanut (Arachis Hypogaea) Flour. Peanut (Arachis Hypogaea) Oil, Hydrogenated Peanut Oil, and Peanut Acid were subsequently included in the safety assessment of plant-derived fatty acid oils (2017), and are therefore not included in this re-review. Additionally, Peanut (Arachis Hypogaea) Flour is not included in this review because ingredients found insufficient are not considered for rereview.

   Because it has been at least 15 years since the safety assessment was published, in accordance with CIR Procedures, the Panel should consider whether the safety assessment of Peanut Glycerides should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1996 forward. No relevant published data were found.

   No reported uses or concentrations of use were reported, according to 2022 FDA VCRP data or a Council survey conducted in 2022, respectively. No reported uses or concentration of use data were reported for Peanut Glycerides in the original report.

   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.

7. Phytantriol – RR (Regina) – ***Dr. Cohen reports on day 2*** – The Panel first published a review on the safety of Phytantriol in 2007, with the conclusion that it is safe as a cosmetic ingredient in the practices of use and concentration as described in that safety assessment.



   Because it has been at least 15 years since the Final Report was published, in accordance with CIR Procedures, the Panel should consider whether the safety assessment of Phytantriol should be reopened. An exhaustive search of the world's literature was performed for studies dated 2000 forward.

   Therein, a case study was found of a 44-year-old woman with no past medical history and no exposure to known irritants presented with an acute eczematous skin reaction on the face after utilizing a face cream with Phytantriol. Patch testing revealed the source of the contact allergy was Phytantriol at concentrations of 0.02-0.5%.

   The frequency of use of Phytantriol has decreased since the original report was issued, from 94 formulations as reported in the 2002 final report to 82 formulations in 2022. The maximum concentration of use reported in response to a 2022 survey is 0.54%. The maximum use concentration reported by industry in 2003 was 0.1%. However, it should be noted that personal communication submitted to CIR in 2004 indicated that the expected use concentration in products under development was 3%; accordingly, the conclusion that was reached in the original report considered use up to 3%.

   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 7 rereview summaries (presented in 1 document) and 1 strategy memo.

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

2. Chloroxylenol – RRsum – (Priya) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider

the rereview summary and finalize it.

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

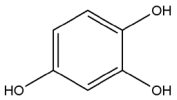
4. Glyceryl Diesters – RRsum – (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

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

6. Acid Orange 3 – RRsum – (Christina) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

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

8. 1,2,4-Trihydroxybenzene – SM (Bart) – ***Dr. Cohen reports on day 2*** – 1,2,4-Trihydroxybenzene is an auto-oxidative hair dye ingredient (i.e., an oxidative hair dye that does not require hydrogen peroxide for oxidation prior to coupling). This hair dye ingredient is banned in the EU and under significant scrutiny in South Korea and elsewhere. ***Would the Panel like to prioritize this ingredient for review in 2023?***



Full Panel Meeting

The Panel will consider the 2 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 7 rereview documents, the 7 rereview summaries, and the 1 strategy memo.

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)~~ ***in-person***!

Agenda
163rd Meeting of the Expert Panel for Cosmetic Ingredient Safety
December 5th – 6th, 2022

Monday, December 5, 2022		
8:30 AM	**WELCOME TO THE 163rd EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:45 AM	**PRESENTATION – Hair Dyes Chemistry and Toxicology**	**Dr. Carsten Goebel (Wella)**
9:45 AM	**TEAM MEETINGS**	**Drs. Cohen/Belsito**

	Dr. Belsito's Team
FR (PC)	Ginger
RR (PC)	Choleth-24
RR (PC)	Brown Algae
TR (RT)	Phytosteryl Glutamates
DR (RT)	*Zanthoxylum piperitum*
DAR (RT)	Octyldodecyl Stearoyl Stearate
RR (RT)	Phytantriol
SM (BH|MF)	1,2,4-Trihydroxybenzene
RRsum (BH|MF)	RR Summaries (all)
RR (CB)	Basic Blue 99
RR (CB)	HC Yellow No. 5
DAR (CB)	6-Amino-*m*-Cresol
DAR (CB)	6-Amino-*o*-Cresol
DR (CB)	Basic Yellow 87
DR (CB)	Olive
FR (PR)	Fatty Ethers
DR (PR)	Mallow
RR (PR)	Methyl Alcohol
RR (PR)	Peanut Glycerides

	Dr. Cohen's Team*
RR (CB)	Basic Blue 99
RR (CB)	HC Yellow No. 5
DAR (CB)	6-Amino-*m*-Cresol
DAR (CB)	6-Amino-*o*-Cresol
DR (CB)	Basic Yellow 87
DR (CB)	Olive
FR (PR)	Fatty Ethers
DR (PR)	Mallow
RR (PR)	Methyl Alcohol
RR (PR)	Peanut Glycerides
FR (PC)	Ginger
RR (PC)	Choleth-24
RR (PC)	Brown Algae
TR (RT)	Phytosteryl Glutamates
DR (RT)	*Zanthoxylum piperitum*
DAR (RT)	Octyldodecyl Stearoyl Stearate
RR (RT)	Phytantriol
RRsum (BH|MF)	RR Summaries (all)
SM (BH|MF)	1,2,4-Trihydroxybenzene

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.

Tuesday, December 6, 2022			
8:30 AM	**WELCOME TO THE 163rd FULL EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:40 AM	Admin	**MINUTES OF THE SEPTEMBER 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 (PR)	Fatty Ethers – ***Dr. Cohen reports***	
	FR (PC)	Ginger - *Zingiber officinale* Ingredients – ***Dr. Belsito reports***	
	Reports Advancing		
	TR (RT)	Phytosteryl Glutamates – ***Dr. Cohen reports***	
	DAR (RT)	Octyldodecyl Stearoyl Stearate – ***Dr. Belsito reports***	
	DR (RT)	*Zanthoxylum piperitum* ingredients – ***Dr. Cohen reports***	
	DR (PR)	Mallow - *Malva sylvestris* ingredients – ***Dr. Belsito reports***	
	DR (CB)	Olive - *Olea europaea* ingredients – ***Dr. Cohen reports***	
	DR (CB)	Basic Yellow 87 – ***Dr. Belsito reports***	
	DAR (CB)	6-Amino-*m*-Cresol – ***Dr. Cohen reports***	
	DAR (CB)	6-Amino-*o*-Cresol – ***Dr. Belsito reports***	
	Other Items		
	RR (CB)	Basic Blue 99 – ***Dr. Cohen reports***	
	RR (CB)	HC Yellow No. 5 – ***Dr. Belsito reports***	
	RR (PR)	Methyl Alcohol – ***Dr. Cohen reports***	
	RR (PR)	Peanut Glycerides – ***Dr. Belsito reports***	
	RR (RT)	Phytantriol – ***Dr. Cohen reports***	
	RR (PC)	Brown Algae – ***Dr. Belsito reports***	
	RR (PC)	Choleth-24 – ***Dr. Cohen reports***	
	RRsum (PC|BH|MF)	Hexamidine – ***Dr. Belsito reports***	
	RRsum (PC|BH|MF)	Chloroxylenol – ***Dr. Cohen reports***	
	RRsum (PR|BH|MF)	Erythorbic Acid – ***Dr. Belsito reports***	
	RRsum (PR|BH|MF)	Glyceryl Diesters – ***Dr. Cohen reports***	
	RRsum (CB|BH|MF)	Sodium Lauryl Sulfoacetate – ***Dr. Belsito reports***	
	RRsum (CB|BH|MF)	Acid Orange 3 – ***Dr. Cohen reports***	
	RRsum (RT|BH|MF)	Mink Oil – ***Dr. Belsito reports***	
	SM (BH)	1,2,4-Trihydroxybenzene – ***Dr. Cohen reports***	

ADJOURN – *The next meeting will be on **March 6 – 7, 2023 (Monday - Tuesday).** Location TBD. 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-SECOND MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

September 26-27, 2022

Microsoft Teams Virtual Meeting

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.

Daniel C. Liebler, 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.

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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 - 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

Name	*Organization*
Irina Agro	Ashland
Nosheen Ahmad	Mary Kay, Inc.
Ivonne Albán	CASIC
Jay Ansell	Personal Care Products Council
John Bailey	JEB Consulting
Nadine Bewry	Sanofi
Don Bjerke	Procter & Gamble
Jeffrey Brown	BASF
Lauren Brown	unidentified
Catherine Casey	unidentified
Liwen Chen	US FDA
Anne Corriou	Givaudan
Vivek Dadhania	Bath & Body Works
Silvia Pérez Damonte	CLAIM
Carol Eisenmann	Personal Care Products Council
Mark Ellis	International Diatomite Producers Assoc.
Christine Mazza Ferreira	unidentified
Fabian Flores	unidentified
Alice Grimes	unidentified
Salwa Ibrahim	DKSH
Sandra James-Yi	Nu Skin Enterprises
Jon Lalko	Estée Lauder
Martha Elena Leal	Mary Kay, Inc.
Ekaterine Kovziridze	TRI-K Industries
Zydnia Madera	E.T. Browne Drug Company, Inc.
Michael Maynard	Beiersdorf
Sylvain Mazalrey	SILAB
Lauren Nardella	The Rose Sheet
Jeffery Nicolai	J Nicolai Law
Hayato Nishida	unidentified
Kimberly Norman	Personal Care Products Council
Edmund O'Brien	L'Oreal USA S/D, Inc.
Stefanie O'Neal	Kao Corp.
Gbemi Oyeti	unidentified
Shanti Pabbathi	CHANEL
Elizabeth Petro	US FDA
Audrey Pokrzywa	SILAB
Carol Pratt	unidentified
Mona Rose	unidentified
Alexandra Gorman Scranton	Women's Voices for the Earth
Daisy Shelton	unidentified
Jannavi Srinivasan	US FDA
Janet Summers	Sanofi
Frances Troy	unidentified
Teresa Washington	unidentified
Michael Wyatt	US FDA
Hong Xie	US FDA
Merle Zimmerman	AHPA
Aleksandra Zmiric	Clariant

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 162nd meeting of the Expert Panel for Cosmetic Ingredient Safety. While this meeting was virtual once again, Dr. Bergfeld announced that the December 2022 meeting will be in-person once again. She welcomed new Panel members, Dr. Susan Tilton, Dr. Allan Rettie, and Dr. David Ross and expressed her appreciation to them for joining the Panel. The Panel is delighted to have them on board! Dr. Bergfeld also announced with regret the resignation of Dr. Dan Liebler from the Panel and thanked him for his service to the Panel.

Dr. Bergfeld also expressed her appreciation towards CIR staff, CIR directors, the CIR Scientific and Support Committee, and the Panel for all their continuing efforts, support, and research. The documents continue to be of high quality.

Dr. Bergfeld stated that the Panel would review 12 ingredient reports, including 4 reports on botanical ingredients, along with 7 abbreviated reviews and 7 rereviews summaries. The administrative items included continued discussion of the format for cosmetic use tables, a review of current boilerplates used in documents, review of the priority list and discussion on the potential inclusion of prostaglandins, and discussion on the strategy on how to review the yeast group of ingredients following a presentation on this group of ingredients. Dr. Bergfeld noted that comments were received from Women's Voices of the Earth on the airbrush boilerplate language and clay ingredients and expressed appreciation to CIR staff for the prepared responses to the comments that the Panel would review.

APPROVAL OF MINUTES

The minutes of the June 16-17, 2022 (161st) Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth noted that CIR is very fortunate to have a new and amazing Panel member join us at this meeting, Dr. Susan Tilton. All agreed that she did a splendid job.

He also noted that when he joined CIR, Dr. Dan Liebler was a rather new addition to the Panel. It is hard to believe that more than a decade has gone by since then, and that Dr. Liebler is now off to run his incorporated proteomics company. Everyone at CIR and on the Expert Panel for Cosmetic Ingredient Safety has greatly appreciated his expertise over the years and has also greatly enjoyed his camaraderie and humor. He will be dearly missed at these meetings.

Dr. Heldreth reiterated his gratitude to each and every one of the members and liaisons for making this Panel what it is. He also remarked about the anticipation to finally see everyone all in-person in December, some of whom it will be the first time in a while and others the very first time ever.

FINAL SAFETY ASSESSMENTS

Diatomaceous Earth

The Panel issued a Final Report with the conclusion that Diatomaceous Earth is safe in cosmetics in the present practices of use and concentration described in the safety assessment. Diatomaceous Earth is a polymorph of silica, or silicon dioxide, and is naturally-occurring. The Panel understands that Diatomaceous Earth, whether unprocessed (natural) or heat-processed (calcined or flux-calcined), can contain crystalline silica, a known respiratory carcinogen. However, the Panel noted that chronic inhalation studies of flux-calcined Diatomaceous Earth (which may comprise up to 60% crystalline silica) were negative for fibrosis or tumors in rats and guinea pigs. These data, coupled with the fact that Diatomaceous Earth is used at relatively low concentrations in cosmetics, mitigated concerns about use in products that may be incidentally inhaled, including face masks which may flake during drying.

Fatty Esters End-Capped Alkoxylates

The Panel issued a Final Report with the conclusion that the following 14 fatty esters end-capped alkoxylates are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

PEG/PPG-8/3 Diisostearate
PEG-15 Butylene Glycol Diisostearate*
PEG-10 Glyceryl Diisostearate*
PEG-15 Glyceryl Diisostearate*
PEG-20 Glyceryl Diisostearate*
PEG-30 Glyceryl Diisostearate*
PEG-60 Glyceryl Diisostearate*
PEG-12 Glyceryl Dimyristate
PEG-12 Glyceryl Dioleate*
PEG-3 Glyceryl Distearate
PEG-4 Glyceryl Distearate*
PEG-12 Glyceryl Distearate
PEG-23 Glyceryl Distearate*
PEG-4 Polyglyceryl-2-Distearate*

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

The Panel noted the lack of developmental and reproductive toxicity data and genotoxicity studies for the fatty ester end-capped alkoxylated ingredients. However, the Panel also noted these ingredients are large molecules (> 1600 Da) and are not likely to absorb readily through the skin. This finding, coupled with the favorable safety profile and lack of structural features associated with genotoxicity, obviated the need for developmental and reproductive toxicity and genotoxicity data.

Glycolactones
The Panel issued a Final Report with the conclusion that Gluconolactone is safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel also concluded that the available data are insufficient to make a determination that the following 4 ingredients are safe under the intended conditions of use in cosmetic formulations:

Galactonolactone*
Glucarolactone*
Glucoheptonolactone*
Ribonolactone*
* *There are currently no uses reported for these ingredients.*

The insufficiencies include impurities data for all 4 insufficient ingredients, and cosmetic-specific method of manufacturing data for Glucarolactone and Glucoheptonolactone.

Hydroxyacetophenone
The Panel issued a Final Report with the conclusion this ingredient is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Previously, the Panel noted that Hydroxyacetophenone is conferred a generally recognized as safe (GRAS) status as a food flavoring substance by the Flavoring, Extract, and Manufacturing Association (FEMA). The Panel determined that systemic exposure to Hydroxyacetophenone would be much higher from consumption in food, relative to use in cosmetics. Systemic toxicity concerns were further mitigated by a high reported purity of 99.5%, low concentrations of use in cosmetics, as well as a favorable toxicological profile and lack of chemical structure alerts for this ingredient. The Panel noted the potential for ocular irritation, evidenced by neat application and testing of a granular substance; and thereby stated that manufacturers should be aware of the potential for ocular irritation when formulating products that contain this ingredient for use near the eye, and that measures should be taken to ensure that these products are not irritating.

Portulaca oleracea
The Panel issued a Final Report with the conclusion that the following 4 *Portulaca oleracea*-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:

Portulaca Oleracea Extract
Portulaca Oleracea Flower/Leaf/Stem Extract*
Portulaca Oleracea Juice*
Portulaca Oleracea 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 safety of these ingredients is supported by the available data on food use, limited systemic exposure from dermal absorption, and negative findings in human dermal irritation and sensitization studies on the whole plant extract. The Panel noted the presence of potentially sensitizing constituents (i.e., terpenes) in the composition of these individual ingredients, though at concentrations below concern; accordingly, the Panel stated that 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.

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

Distarch Phosphate Distarch Phosphate Acetate* Hydroxypropyl Starch Phosphate Sodium Hydroxypropyl Starch Phosphate
**Not reported to be in current use. Were this ingredient in this group not in current to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

The Panel noted that new data received on Sodium Hydroxypropyl Starch Phosphate. However, this data did not change their conclusion.

TENTATIVE SAFETY ASSESSMENTS

Naturally-Sourced Clays
The Panel issued a Tentative Amended Report for public comment with the conclusion that Kaolin* is safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel noted that Kaolin is reported to be used in products which may be incidentally inhaled, including face powders at up to 15%; however, the data available from inhalation studies, including acute, chronic, and carcinogenicity data, suggest little potential for adverse respiratory effects at relevant doses.

The Panel also concluded that the following 7 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 that these ingredients are safe in products that may be incidentally inhaled.

Attapulgite*
Bentonite*
Clay
Fuller's Earth*
Hectorite*
Illite
Montmorillonite*
**Previously reviewed by the Panel.*

Because of the potential for crystalline silica to be an impurity and the absence of repeated-dose inhalation data for these 7 ingredients, the additional data needed to determine the safety of the use of these ingredients in formulations that may be incidentally inhaled include:

- Composition and impurities data, specifically, quantification of crystalline silica content
- Chronic inhalation studies

The Panel was also made aware that nanoforms of clay ingredients could potentially be used in cosmetic formulations, including those that could result in incidental ingestion (e.g., lipstick and toothpaste). However, use of nanoform ingredients does not translate into nanoform final formulations. In these formulations, low concentrations of use (e.g., maximum reported use concentration of Kaolin in lipstick is 14.5%) and processing would be expected to result in much larger particle sizes (by, for example, agglomeration) in the consumer product.

Polyhydroxystearic Acid
The Panel issued a Tentative Report for public comment with the conclusion that the following 3 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Polyhydroxystearic Acid Poly(3-Hydroxyoctanoic Acid)* Polylactic Acid
**Not reported to be in current use. Were the ingredient in this group not in current use 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.*

According to 2022 Voluntary Cosmetic Registration Program data and the results from a concentration of use survey completed by the Personal Care Products Council in 2021, Polyhydroxystearic Acid has 265 reported uses and is used at up to 14.2% (in lipsticks) and Polylactic Acid has 18 reported uses and is used at up to 5% (in skin cleansing products). The Panel discussed that these are large molecules, which are not likely to be absorbed. Additionally, the Panel considered the prior safety assessments of the corresponding monomers of these ingredients, and surmised that the systemic toxicity of these polymers would not be different. The Panel was further reassured of the dermal safety of these ingredients by the US Food and Drug Administration (FDA)-approved uses of Polylactic Acid in medical devices, as well as the existing American Society for Testing Materials (ASTM) International standard for this ingredient.

Rosa centifolia
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 concentrations described in the safety assessment when formulated to be non-sensitizing:

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

The Panel noted that the flower and bud derived ingredients that are reviewed in this safety assessment are found in foods that are GRAS. Composition and other data on the stem extract denote similarities to both the flower and the bud and obviate the need for additional toxicological data. These findings provided sufficient data for the Panel to conclude on the safety of flower-, bud-, and stem-derived ingredients. The Panel noted the presence of citronellol and geraniol, 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.

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

Rosa Centifolia Callus Culture Extract **
Rosa Centifolia Extract **
Rosa Centifolia Leaf Cell Extract **
***There are currently no uses reported for these ingredients.*

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

- Method of manufacture
- Composition and impurities data
- 28-day dermal toxicity data
    - if positive additional toxicological endpoints may be needed
- Dermal irritation and sensitization data.

Trisodium Ethylenediamine Disuccinate
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 as described in the safety assessment. The Panel determined that the available impurities, systemic toxicity, ocular irritation, and dermal irritation/sensitization data were sufficient to support the safety of these ingredients. The Panel noted mutagenicity in an vitro mammalian chromosomal aberration assay performed on Trisodium Ethylenediamine Disuccinate. However, concern for this result was mitigated as mutagenicity was only observed under specific conditions (without metabolic activation, 42-h incubation), and several other in vitro and in vivo genotoxicity assays had negative results.

INSUFFICIENT DATA ANNOUNCEMENT

Phenyl-Substituted Methicones
The Panel issued an Insufficient Data Announcement (IDA) for these 7 phenyl-substituted methicone ingredients:

Diphenyl Dimethicone
Diphenylsiloxy Phenyl Trimethicone
Diphenylsiloxy Phenyl/Propyl Trimethicone
Phenyl Dimethicone
Phenyl Methicone
Phenyl Trimethicone
Trimethylsiloxyphenyl Dimethicone

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

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

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 7 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.

- Octyldodecyl Stearoyl Stearate – 1 ingredient

In contrast, the Panel reaffirmed the conclusions reached for the following 7 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.

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

Additionally, the Panel reconsidered its previous decision to reopen the following safety assessment. A re-review summary will be presented to the Panel for this safety assessment at an upcoming meeting.

- Acid Orange 3 – 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:

- Amyl Acetate – 2 ingredients
- Cottonseed Glyceride – 2 ingredients
- Glycol Stearate – 2 ingredients
- *N*,*N*-Bis(2-Hydroxyethyl-p-Phenylenediamine Sulfate – 1 ingredient
- PEGs Soy Sterol – 6 ingredients
- Polyacrylamide – 1 ingredient
- PPGs Stearyl Ether – 2 ingredients

2023 PRIORITIES

The priority list is typically based on stakeholder requests ("for cause," e.g., a hair dye) and FOU data from FDA's VCRP; this year, VCRP data were received from the FDA on January 11 (in response to a Freedom of Information Act request).

While this list includes only the lead ingredients, groupings of ingredients were drafted in the meeting materials. The Panel considered these groupings and took no issue. These grouping may be found here https://www.cir-safety.org/about

There are 17 reports proposed (2 of the "per FOU" ingredients below are proposed to be reviewed together in 1 report) on the 2023 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 Final Priorities List

Ingredients	Frequency of Use (FOU) Data Year 2022
For cause	
HC Blue No. 15	**22**
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**

STRATEGY MEMO – RE-REVIEW OF INGREDIENTS WITH NO REPORTED USE

A strategy memo was presented to the Panel, asking whether no reported frequency of use (FOU = 0) was sufficient reason to not reopen a previously-issued safety assessment that was due for re-review. The Panel stated that it is not, and that all previous safety assessment due for re-review are to be considered by the Panel, regardless of FOU.

USE TABLE FORMAT

The Panel reviewed proposed changes to the Use Table format that is utilized in each report. Panel members stated that, at this time, they are not inclined to make changes to the existing Use Table format, which employs a summary of frequency and concentration of use based on duration of use and exposure type. Specifically, the Panel finds the summary information delivers a concise summary of this information as they review the report. However, it was requested that the existing format and the proposed format (which would articulate both frequency and concentration of use by individual product category) be provided concurrently in a Draft Report in order for the Panel to consider the functionality of each. Additionally, it has been requested that the journal be queried that, if the existing (summary) use table format is maintained, is it possible for an additional table that describes frequency and concentration of use for each product category be included as a supplement to the report upon publication.

REPORT FORMAT AND SOPs DISCUSSION

The Panel was presented with the report format outline and a compilation of all current and previous boilerplate/guidance documents used as standard operating procedures (SOPs). Changes to some of the boilerplate language were suggested.

PRESENTATION AND STRATEGY MEMO – YEAST-DERIVED INGREDIENTS

A thorough and insightful presentation on yeast-derived cosmetic ingredients was provided by Dr. Pokrzywa and Dr. Mazalrey, of Silab. The purpose of the presentation was to impart information on the strains of yeast used in cosmetic ingredients, as well as the processes used in manufacturing such ingredients, thereby aiding in the development of the group of ingredients to be reviewed in the resulting safety assessment. This presentation has been added to the meeting page https://www.cir-safety.org/meeting/162nd-expert-panel-meeting.

The Panel discussed the strategy of grouping the yeast-derived ingredients for the safety evaluation by considering the taxonomy, identification and analytical characterization, biosafety level (BSL) classification, as well as the unique cosmetic ingredient manufacturing processes. The Panel further discussed the critical elements that may contribute to the development of the resulting safety assessment, such as VCRP data, marketing information supplemented by industry submissions, and food use data (including GRAS status as determined by FDA), as well as the importance of distinguishing the pathogenic yeasts of the *Saccharomycetes* class (which would not be included) and those with BSL-1 confirmation (which would be included).

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, PhD, Executive Director, CIR
Date: November 10, 2022
Subject: Strategy Memo on 1,2,4-Trihydroxybenzene

In October, CIR staff met with leaders of the Korean Cosmetic Association and the Japan Cosmetic Industry Association. In November, CIR staff presented at the Korean Society of Toxicology. In both instances, CIR was made aware of struggles 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.

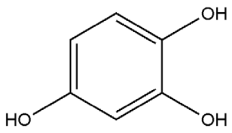

Figure 1. 1,2,4-Trihydroxybenzene

According to 2022 VCRP data, this ingredient is currently used in 23 formulations in the US. Please remember that, with regard to hair dye ingredients, frequency of use (FOU) is a particularly poor surrogate of how many consumers are exposed. Most commonly used hair dye ingredients have similar FOU.

Accordingly, would the Panel like to prioritize this ingredient for review in 2023?

References

1. Scientific Committee on Consumer Safety (SCCS) Opinion on hair dye 1,2,4-trihydroxybenzene (1,2,4-THB); European Commission; Published 2019; Accessed November 10, 2020. https://health.ec.europa.eu/system/files/2021-08/sccs_o_222_0.pdf Report No. SCCS/1598/18

2. "Risk Assessment and Scientific Opinion of 1,2,4-Trihydroxybenzene (THB)," Dr. Qasim Chaudhry, The 38th Annual Meeting of Korean Society of Toxicology/Korean Environmental Mutagen Society (KSOT/KEMS), Chemical and Human Health, November 7, 2022, Seoul, Republic of Korea.

3. European Commission. (2020). Commission Regulation (EU) 2020/1683 of 12 November 2020 amending Annexes II and III to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products. Retrieved on 03/06/2022 from https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R1683&from=EN