ADMIN

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EXPERT PANEL MEETING
June 12-13, 2023

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: 165th Meeting of the Expert Panel — Monday and Tuesday, June 12th-13th, 2023
Date: May 19, 2023

Welcome to the second Panel Meeting of 2023! The agenda and accompanying materials for the 165th Expert Panel Meeting, to be held on June 12-13, 2023, are now available. Please note that this meeting is on a ***Monday and Tuesday***. This meeting will be held in-person at the Melrose Georgetown Hotel, 2430 Pennsylvania Avenue NW, Washington, DC 20037. We will have 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/165th-expert-panel-meeting

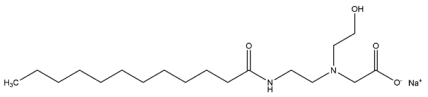
The meeting agenda includes the consideration of 13 reports advancing in the review process, including 3 final reports, 5 tentative report, and 5 draft reports. Also on the agenda, are 8 rereview documents (5 proposals for rereview and 3 rereview summaries). ***In each case of a rereview proposal, the 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 3 administrative documents, including a Format/SOP update prepared by Monice, a Draft Nitrosation Resource Document prepared by Jinqiu, and a proposed amendment to the Draft 2024 Priorities.

Just for your information, while CIR was able to obtain updated frequency of use information earlier this year, the FDA VCRP has since come to an end. With the changes to be implemented as part of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), FDA has chosen to start afresh with a separate and distinct mandatory reporting program; more to come on this as we are aware.

Team Meetings

Draft Report - There are 5 draft reports for review. - Sufficient data to proceed, or issue an Insufficient Data Announcement (IDA)?

1. Fatty Amphocarboxylates – DR (Priya) – ***Dr. Belsito reports on day 2*** – This is the first time the Panel is reviewing this safety assessment of the following 11 fatty amphocarboxylates:



Disodium Cocoamphodiacetate
Disodium Cocoamphodipropionate
Disodium Lauroamphodiacetate
Disodium Wheatgermamphodiacetate
Sodium Arganamphoacetate
Sodium Cocoamphoacetate
Sodium Cocoamphopropionate
Sodium Cottonseedamphoacetate
Sodium Lauroamphoacetate
Sodium Olivamphoacetate
Sodium Sweetalmondamphoacetate

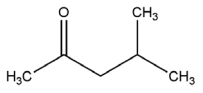
Sodium Lauroamphoacetate was included on the 2021 Priority List due to high reported frequencies of use. It was noted that 4 related ingredients previously reviewed by the Panel in a report published in 1990 and re-reviewed in 2008, i.e., Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate, would soon be considered for another re-review. Accordingly, the Panel deemed it appropriate to include the 4 previously-reviewed ingredients in this new safety assessment. (The Panel had concluded that these 4 ingredients are safe in cosmetics in the present practices of use and concentration, as described in the 1990 safety assessment.)

According to 2023 FDA VCRP data, Sodium Lauroamphoacetate is reported to be used in 202 total formulations (183 rinse-off formulations; 17 rinse-off formulations; and 2 formulations diluted for bath use). Disodium Cocoamphodiacetate has the highest frequency of use (220 total formulations; 40 leave-on formulations, 179 rinse-off formulations, and 1 formulation diluted for bath use). The number of uses for this ingredient has increased since it was last reviewed; it was previously reported to be used in 194 formulations in 2005. Sodium Cocoamphoacetate is reported to be used in 121 formulations, and all other ingredients are reported to be used in 73 formulations or less. The results of the concentration of use survey initiated by the Council in 2021 indicate that Disodium Cocoamphodiacetate has the highest concentration of use in rinse-off products; it is used at up to 20% in cleansing products. Disodium Lauroamphodiacetate has the highest concentration of use reported in leave-on products; it is used at up to 5.4% in other hair preparations. In 2006, the ingredient with the highest reported concentration of use was Sodium Cocoamphoacetate (used at up to 18% in bath soaps and detergents).

Several of these ingredients are reported to be used in products that are applied near the eye; for example, Sodium Lauroamphoacetate is used at 1.3% in eye makeup removers. In addition, these ingredients are reported to be used in products that may result in mucous membrane exposure (e.g., Disodium Cocoamphodiacetate is reported to be used in other personal cleanliness products at up to 3.3%) and in baby products (Disodium Cocoamphodiacetate is used in baby shampoos at up to 5.4%). Disodium Lauroamphodiacetate is used in a perfume (concentration not reported) and could possibly be inhaled.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

2. MIBK – DAR (Regina) – ***Dr. Cohen reports on day 2*** – In its initial assessment of MIBK, the Panel found that MIBK is safe as used in nail polish removers and as an alcohol denaturant in cosmetic products. In March 2023, the Panel reopened the safety assessment of this ingredient. In its decision to reopen the assessment, the Panel considered new carcinogenicity and toxicological data provided by the National Toxicology Program (NTP), this study was in progress at the time of the original review of MIBK.

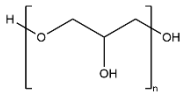


According to 2023 VCRP data, MIBK is reported to be used in 2 formulations (Other Manicuring

Preparations and Aftershave Lotion). In the 2022 Personal Care Products Council concentration of use survey, no uses were reported.

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. Polyglycerins – DR (Preethi) – ***Dr. Cohen reports on day 2*** - This is the first time the Panel has seen a safety assessment of Diglycerin and Polyglycerin-3, -6, and -10. A Scientific Literature Review (SLR) was announced on March 9, 2023.

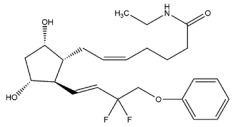


The Panel has previously reviewed the safety of glycerin; in 2019, a final report was published with the conclusion that glycerin is safe as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment. Of note, the European Chemicals Agency (ECHA) dossiers for these polyglycerins use studies on glycerin and polyglycerol polyricinoleate as read-across sources to address the repeated dose toxicity, developmental and reproductive toxicity, and carcinogenicity endpoints for ingredients in this report. ***Does the Panel agree with the use of these chemicals as read-across sources?***

According to 2023 VCRP survey data, Diglycerin is reported to be used in 222 formulations and Polyglycerin-3 is reported to be used in 221 formulations. The results of the concentration of use survey conducted by the Council in 2022 indicate Diglycerin has the highest concentration of use; it is used at up to 28% in skin cleansing products. The highest concentration of use reported for products resulting in leave-on dermal exposure is 5% Diglycerin in face and neck products. A few of these ingredients are reported to be used in products that may lead to incidental ocular exposure and to incidental ingestion. For example, Diglycerin is reported to be used at up to 3% in eye lotions, and it is used at up to 3.6% in lipstick formulations.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data are deemed insufficient, the Panel should issue an IDA, specifying the data needs therein.

4. Prostaglandins – DR (Priya) – ***Dr. Belsito reports on day 2*** – This is the first time the Panel has seen a safety assessment of Ethyl Tafluprostamide and Isopropyl Cloprostenate. Due to a lack of relevant published data, a Scientific Literature Review Notice to Proceed (NTP) was issued for these ingredients on March 17, 2023. Since the issuing of the NTP, several in vitro and in vivo ocular irritation studies, as well as HRIPTs performed using products containing Isopropyl Cloprostenate, have been received and incorporated into this draft. The majority of studies yielded negative results (or predictions of negative results).



In addition, relevant data were included in the CIR report from an SCCS opinion on prostaglandins and prostaglandin-analogues (including Ethyl Tafluprostamide and Isopropyl Cloprostenate) used in cosmetic products. The SCCS was not able to conclude on the safety of Isopropyl Cloprostenate and Ethyl Tafluprostamide due to a lack of data on these ingredients. Although data were available for cloprostenol and R-cloprostenol, the SCCS determined that drawing conclusions on the toxicokinetics profile of Isopropyl Cloprostenate from the toxicokinetics data on cloprostenol and R-cloprostenol would not be appropriate, as the systemic uptake and bioavailability/distribution would differ between Isopropyl Cloprostenate and cloprostenol/R-cloprostenol. ***Does the Panel agree that data on cloprostenol are not appropriate for inclusion in the report, because the data cannot be read across to Isopropyl Cloprostenate?***

Three uses (all of which are “other eye makeup preparations”) are reported for Isopropyl Cloprostenate, according to 2023 FDA VCRP data. (Frequency of use data for Ethyl Tafluprostamide were not reported in the VCRP.) Concentrations of use were not received for either Ethyl Tafluprostamide or Isopropyl Cloprostenate in response to a survey initiated by the Council in 2022. However, unpublished data reporting calculations of the concentration of Isopropyl Cloprostenate in two eyelash serums were received and are included herein; these serums were reported to contain 0.0044% and 0.0048% Isopropyl Cloprostenate, respectively. In addition, unpublished data on Ethyl Tafluprostamide indicate that this ingredient is used in products intended for use on eyelashes,

eyebrows, or scalp hair, at concentrations ranging from 0.012 to 0.2%.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA specifying the data needs therein.

5. Yeast - RevDR (Priya) – ***Dr. Cohen reports on day 2*** - At the September 2021 meeting, the Panel reviewed the Draft Report on the following 8 yeast-derived ingredients:

Hydrolyzed Yeast	Yeast Beta-Glucan
Hydrolyzed Yeast Extract	Yeast Extract
Hydrolyzed Yeast Protein	Yeast Polysaccharides
Yeast	Saccharomyces Cerevisiae Extract

As the definition of Yeast given in the *International Cosmetic Ingredient Dictionary and Handbook* is extremely broad, the Panel issued an IDA for this ingredient group and requested clarification on the species of yeast used in the manufacturing of these ingredients for use cosmetics. At the time the IDA was issued and until February 2022, *Saccharomyces cerevisiae* was thought to be the predominant species used in the preparation of these yeast-derived ingredients. However, on February 7, 2022, summary information on Yeast Extract derived from several other species of yeast belonging to the Saccharomycetes class (e.g., *Pichia anomala*) was received from Council. Because of this new information, at the March 2022 meeting, a strategy memo was issued asking the Panel for guidance as to whether the report should review only *Saccharomyces cerevisiae*-derived ingredients, or, if ingredients derived from other species of yeast under the Saccharomycetes class (e.g., Pichia Anomala Extract) should also be reviewed. The Panel suggested the preparation of another strategy memo, including all yeast ingredients currently listed in the *Dictionary*, along with notations of whether or not these ingredients (or their corresponding species) are used in foods, and their frequency of use in cosmetics. The Panel also requested the guidance of an expert with knowledge regarding the classification and general biology of yeasts, and again requested verification from industry on which yeast species are used in the manufacturing of the generic yeast ingredients (e.g., Yeast Extract).

At the September 2022 meeting, an expert presented on the manufacturing, general characteristics, and classification of yeast-derived cosmetic ingredients. The Panel reviewed the list of all yeast-derived ingredients present in the *Dictionary* and determined that a Revised Draft Report should be prepared on all ingredients (regardless of frequency of use).

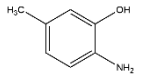
Accordingly, the Revised Draft Report on 56 yeast-derived ingredients is presented for the first time at this meeting. Unfortunately, no verification has been provided by industry regarding all the species of yeast that can be used in the production of the generic yeast ingredients. However, three data submissions were received on Yeast Extract, and the genus and species of yeasts (there were several) that were used to derive the Yeast Extract named as the test article in each submission were identified. Based on personal communication with the Council, even though Yeast Extract was identified as the INCI name, it was determined that those data should be associated with the specific ingredients derived from the genus and species named in those submissions. (For example, sensitization data on Yeast Extract derived from *Pichia anomala* are summarized in the report as a study on Pichia Anomala Extract.)

According to 2023 VCRP survey data, Yeast Extract is reported to be used in 398 formulations (343 leave-on formulations and 55 rinse-off formulations). All other in-use ingredients are reported to be used in 81 formulations or less. The results of the concentration of use survey conducted by the Council indicate Galactomyces Ferment Filtrate has the highest concentration of use in a leave-on formulation; it is used at up to 90.7% in moisturizing products (not spray).

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue a second IDA, specifying the data needs therein.

Draft Tentative Report - There are 5 draft tentative reports for consideration. - Issue a tentative conclusion?

1. 6-Amino-*m*-Cresol – TAR (Christina) – ***Dr. Belsito reports on day 2*** – At the December 2022 meeting, the Panel determined that the data were insufficient to support safety of this hair dye ingredient and issued an IDA. The additional data needs are:



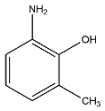
   - Method of manufacture data
   - in vivo genotoxicity studies

   Since the IDA, CIR has received no new data. The 2023 VCRP survey data reports that there are no uses for this ingredient; last year, there were 2 reported uses in hair dyes. However, please note that concentration of use data (0.69% in hair dyes and colors) were submitted in response to the Council survey, which indicate at least one use.

   The relevancy of the airbrush boilerplate language in hair dye reports has been questioned and a request was made to remove the boilerplate language in the Use section of this report. While this type of use is not reported in the VCRP or in the Council's concentration of use survey, CIR staff has been made aware that airbrush application of hair dye products are being advertised and sold on the Internet. ***The Panel should discuss whether the airbrush boilerplate language should continue to be added to hair dye reports or discontinued.***

   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 Amended Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

2. 6-Amino-*o*-Cresol – TAR (Christina) – ***Dr. Cohen reports on day 2*** – At the December 2022 meeting, the Panel determined that the data were insufficient to support safety of this hair dye ingredient, and issued an IDA. The additional data needs are:



   - Method of manufacture
   - Composition and impurities
   - Concentration of use
   - Absorption, distribution, metabolism, and excretion studies
     - If absorbed, developmental and reproductive toxicity studies, genotoxicity studies, and potentially other endpoints

   Since the IDA, CIR has received no new data. The 2023 VCRP survey data, like the 2022 survey, have no reported uses for 6-Amino-*o*-Cresol. ***As above, the Panel should discuss whether the airbrush boilerplate language should continue to be added to hair dye reports or discontinued.***

   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 Amended Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

3. Olive – TR (Christina) – ***Dr. Cohen reports on day 2*** – At the December 2022 meeting, the Panel issued an IDA. The additional data needed to determine safety for these 23 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

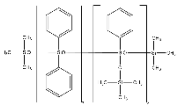
- Composition and impurities data for Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, Hydrolyzed Olive Leaf Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Flower Water, Olea Europaea (Olive) Fruit Unsaponifiables, Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) 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.

Due ot the complexity of the IDA, the data needs are summarized per ingredient in a table immediately following the memo to aid in the Panel's review.

Since the issuance of the IDA, some data were received in response for Olea Europaea (Olive) Fruit Extract. Additionally, use information has been updated with the 2023 VCRP survey data. Changes in the number of uses were minimal. The most notable changes were 1 use now being reported for Olea Europaea (Olive) Bud Extract (no use reported previously) and use no longer being reported for Olea Europaea (Olive) Seed (previously reported with 2 uses). No uses were reported in the results of the concentration of use survey conducted by the Council on the 3 hydrolyzed olive ingredients that were added to the report in December 2022. In addition to concentration of use survey data, the Council provided summary information on an aqueous solution composed of 2.2% Olea Europaea (Olive) Fruit Extract that included animal dermal irritation and sensitization data and in vitro and animal ocular data.

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.

4. Phenyl-Substituted Methicones – TR (Preethi) – ***Dr. Belsito reports on day 2*** –



This is the third time the Panel is seeing a safety assessment of these 7 cosmetic ingredients. At the March 2023 meeting, a Draft Tentative Report was presented to the Panel and new data were provided in a Wave 2 submission from the Silicones, Environmental, Health and Safety Center (SEHSC). However, upon reviewing this data, the Panel issued a second IDA for the following data needs:

- Clarification of the identity and chemical nomenclature for test substances referred to in the SEHSC data submission
- Applicability of these data for use in this assessment
- Additional respiratory toxicity data at, or above, the reported maximum concentration of use in inhaled exposures near the face (Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    - Preferably, the protocol should be similar to the short-term inhalation study of rats exposed to an aerosol containing 3% Phenyl Trimethicone that is described in the original report (30-s burst, followed by a 15-min exposure within a chamber)

Subsequently, the SEHSC confirmed that the test article referred to as phenyl silsesquioxanes is, in fact, Phenyl Trimethicone. Accordingly, data that have been verified in response to the IDA have been incorporated in the report as such.

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.

5. <u>*Zanthoxylum piperitum*</u> – TR (Regina) – ***Dr. Belsito reports on day 2*** – At its initial review in December 2022, the Panel issued an IDA for these 4 *Zanthoxylum piperitum*-derived ingredients. In order to come to a conclusion of safety for these cosmetic ingredients, the following additional data are needed:

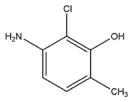
   - Method of manufacture and composition for Zanthoxylum Piperitum Fruit Extract and Zanthoxylum Peel Water.
   - Impurities data for Zanthoxylum Piperitum Peel Water.
   - Further concentration of use data, if available.

   At the December 2022 meeting, Dr. Belsito provided CIR with additional published studies on *Zanthoxylum piperitum*-derived ingredients. These data, consisting primarily of additional composition details, have been incorporated into this iteration of the report. Additional references were also identified within the provided studies as possible sources of relevant information. Please consider which of these are relevant for use in the report.

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

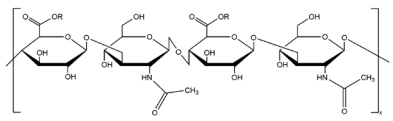
1. <u>5-Amino-6-Chloro-*o*-Cresol</u> – FAR (Christina) – ***Dr. Cohen reports on day 2*** – At the March 2023 meeting, the Panel issued a Tentative Amended Report with the conclusion that 5-Amino-6-Chloro-*o*-Cresol is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment.



   Since the March meeting, CIR has received no new unpublished data. The 2013 opinion from the SCCS, which states that *the on-head concentrations of 1.0% in oxidative hair dyes and 0.5% in non-oxidative hair dye do not pose a risk to the health of the consumer*, has been incorporated in this report (this supersedes a previous opinion which stated that the on-head concentration of 2.0% under oxidative and non-oxidative conditions poses a risk to the health of the consumer), as was as an additional dermal absorption study and an updated margin or safety calculation. The use information has been updated with 2023 VCRP data; uses for 5-Amino-6-Chloro-*o*-Cresol have decreased from 27 to 20.

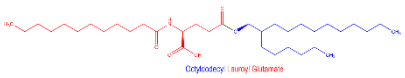
   As above, the Panel should discuss whether the airbrush boilerplate language should continue to be added to hair dye reports or discontinued. After carefully reviewing the Abstract, Discussion, and Conclusion, the Panel should be prepared to issue a Final Amended Report.

2. <u>Hyaluronates</u> – FR (Priya) – ***Dr. Cohen reports on day 2*** – At the March 2023 meeting, the Panel issued a Tentative Report for public comment with the conclusion that Hyaluronic Acid, Hydrolyzed Calcium Hyaluronate, Hydrolyzed Hyaluronic Acid, Hydrolyzed Sodium Hyaluronate, Potassium Hyaluronate, Sodium Acetylated Hyaluronate, and Sodium Hyaluronate 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. 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. Phytosteryl Glutamates – FR (Regina) – ***Dr. Belsito reports on day 2*** – At the December 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that the available data are insufficient to make a determination that the 3 phytosteryl glutamates are safe under the intended conditions of use in cosmetic formulations. In order to come to a conclusion of safety for these cosmetic ingredients, the following additional data are needed:



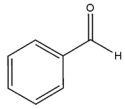
- Method of manufacture
- Impurities data
- 28-day dermal toxicity
    - If positive, other toxicological endpoints, such as developmental and reproductive toxicity, genotoxicity, and carcinogenicity data, may be needed.
- Irritation and sensitization data at maximum reported concentration of use.
- Ocular irritation data, if available

Since the issuing of the Tentative Report, published data on plant sterols and sitosterolemia, 2023 VCRP data, and unpublished method of manufacture and safety data submitted by the Council, have been incorporated into the Draft Final Report. The Panel should review comments on the Tentative Report submitted by the CIR Science and Support Committee (SSC) regarding the request for a dermal 28-d study, in light of having a negative oral 28-d study.

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. However, if the submitted data resolve the needs identified above, the Panel should reconsider the Discussion and Conclusion and issue a revised Tentative Report.

Abbreviated Rereviews (i.e., rereview proposals) – There are 5 rereview documents – In each case, the Panel is only being asked if the report should be reopened.

1. Benzaldehyde – RR (Preethi) – ***Dr. Belsito reports on day 2*** – The Panel first published a review of the safety of Benzaldehyde in 2006. On the basis of data presented in the report, the Panel concluded that Benzaldehyde is safe as used in cosmetic products.

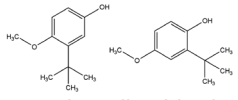


Data on the daily intake, FEMA GRAS status, concentration limits in finished cosmetic products, acute oral toxicity, acute inhalation toxicity, oral developmental and reproductive toxicity, in vitro genotoxicity, acute dermal irritation, and 2 guinea pig maximization tests were found. None of the newly found data were notably different from data in the 2006 report. Because it has been at least 15 years since it was finalized, in accordance with CIR Procedures, the Panel should consider whether the safety assessment of Benzaldehyde should be reopened.

According to 2023 FDA VCRP data, Benzaldehyde has 6 reported uses, a minor change from the 7 reported uses in 2001. Reported use categories have not changed significantly and concentrations of use have remained constant over time. In 2023, the maximum reported concentration of use for Benzaldehyde is 0.2% in non-spray face and neck products, and, in 2001, Benzaldehyde was reported to be used at a maximum concentration of 0.5% in perfumes.

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, confirming the original conclusion, will be presented at an upcoming meeting.

2. BHA – RR (Preethi) – ***Dr. Belsito reports on day 2*** – The Panel first published a review of the safety of Butylated Hydroxyanisole (since renamed as BHA) in 1984. On the basis of the available information presented in the report, the Panel concluded that BHA is safe as a cosmetic ingredient in the present practices of use as described in the safety assessment. The Panel previously considered a re-review of this report and reaffirmed the 1984 conclusion, as published in 2006. Because it has been at least 15 years since it was finalized, in accordance with CIR Procedures, the Panel should again consider whether the safety assessment of BHA should be reopened.



A number of studies evaluating endocrine activity as well as reproductive and developmental effects of BHA, both in vitro and in vivo, have been found. A few oral toxicokinetic studies, several repeated oral dose toxicity studies, 2 Ames tests, a study on the immunomodulatory effects of BHA in mice, another study on the anti-carcinogenicity effects of BHA in rats, and a Dutch cohort study examining the association between the dietary intake of BHA and stomach cancer risk, were also found. Of note, the *Dictionary* defines BHA as a mixture of *tert*-butylated 4-hydroxyanisole isomers which consists chiefly of 3-*tert*-butyl-4-hydroxyanisole with lesser amounts of 2-*tert*-butyl-4-hydroxyanisole. Thus, data found on BHA in both isomeric forms has been included (and identified).

According to 2023 FDA VCRP data, BHA has 70 reported uses; at the time this ingredient was last considered for re-review, 1224 uses were reported. Reported use categories have not changed significantly and concentrations of use have remained constant over time. In 2023, the maximum reported concentration of use for BHA is reported to be 0.15% in other manicuring preparations, while BHA was reported to be used at 0.2% in several product formulations (cologne and toilet waters, perfumes, blushers, and lipstick) in 2003.

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, confirming the original conclusion, will be presented at an upcoming meeting.

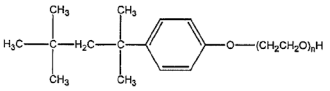
3. Lanolin – RR (Christina) – ***Dr. Belsito reports on day 2*** – The Panel first published a review on the safety of Acetylated Lanolin Alcohol and Related Compounds in 1980. The Panel stated that "based on the available animal data and human experience, the Panel concludes that Lanolin and related Lanolin materials… are 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 on 9 ingredients and reaffirmed the 1980 conclusion, as published in 2005. Because it has been 15 years since the previous re-review was published, in accordance with CIR Procedures, the Panel should again consider whether this safety assessment should be reopened.

Many new studies have been identified in the published literature, with the majority describing the allergenicity to Lanolin and Lanolin Alcohol in patch tests. Lanolin was named the 2023 Contact Allergen of the Year by the American Contact Dermatitis Society.

Since the initial re-review was considered, the frequency of use for Lanolin has decreased from 782 to 285 uses; the majority of uses are in leave-on products. In 2002, the maximum concentration of use for this ingredient was reported to be 37% in leave-on products and 16% in rinse-off products. According to the Council's survey in 2022, the maximum concentration of use in leave-on products is 40% and 10% in rinse-off products. The frequency of use for the other Lanolin-derived ingredients have significantly decreased while most of the maximum concentrations of use have remained approximately the same.

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, confirming the original conclusion, will be presented at an upcoming meeting.

4. Octoxynols – RR (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of 25 octoxynol ingredients, in 2004, with the conclusion that Octoxynol-9, -10, -11, -12, -13, -16, -20, -25, -30, -33, -40, and -70, Octoxynol-9 Carboxylic Acid, Octoxynol-20 Carboxylic Acid, Potassium Octoxynol-12 Phosphate, and Sodium Octoxynol-9 Sulfate are safe as used in rinse-off and leave-on cosmetic products. The Panel also concluded that Octoxynol-1, -3, -5, -6, -7, and -8, Sodium Octoxynol-2 Ethane Sulfonate, Sodium Octoxynol-2 Sulfate, and Sodium Octoxynol-6 Sulfate are safe as used in rinse-off cosmetic products and safe at concentrations of ≤ 5% in leave-on cosmetic products. Because it has been at least 15 years since the final report was published, in accordance with the Procedures, the Panel should consider whether the safety assessment of these octoxynol ingredients should be reopened.

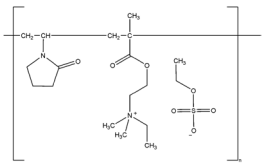


Octoxynol-40 now has an FDA-approved use as an inactive ingredient in an ophthalmic solution at 0.05% w/v. No relevant new toxicological data were found. Both the reported frequency of use and

concentration of use have decreased since the last review. In 2001, the ingredient with the greatest frequency of use was Octoxynol-9, with 131 uses; in 2023, all the octoxynols are reported to be used in 8 formulations or less. The maximum reported concentration of use in 2001 was 25% Octoxynol-10 in hair lighteners with color; the highest leave-on concentration reported was 5% Octoxynol-9 in cologne and toilet water. In 2022, the highest concentration of use reported was 2% Octoxynol-9 in skin cleansing preparations; the only other ingredient for which concentration of use was reported was Octoxynol-12 (1.5% in face and neck preparations). However, Octoxynol-9 is now reported to be used at 0.1% in other baby products, a previously unreported use category for these ingredients.

Of note, the Panel has published reviews on the safety of nonoxynols, which are similar, but slightly longer chain ingredients, in 1983, 1999, and in 2015. During the 2015 review, the Panel concluded that the nonoxynols are safe in the present practices of use and concentration in cosmetics as described in the safety assessment, when formulated to be non-irritating.

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, confirming the original conclusion, will be presented at an upcoming meeting.

5. Polyquaternium-11 – RR (Regina) – ***Dr. Cohen reports on day 2*** – 
The Panel first published a review of the safety of Polyquaternium-11, in 1983. The Panel concluded that Polyquaternium-11 is safe as a cosmetic ingredient in the present practices of use as described in the safety assessment. This conclusion was reaffirmed, as published in 2003. Because it has been at least 15 years since the previous re-review was published, in accordance with the Procedures, the Panel should again consider whether this safety assessment should be reopened.

   No new toxicological studies were found. The frequency and concentration of use of Polyquaternium-11 has decreased since this ingredient was last considered for re-review. According to 2023 frequency of use and concentration of use data, Polyquaternium-11 is reported to be used in 192 formulations at up to 2.9% in leave-on products; in 2001, it was reported to be used in 254 formulations at up to 12% in rinse-off 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.

Administrative Items - there are 3 rereview summaries (presented in 1 document) and 3 other administrative items.

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

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

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

4. Nitrosation Resource Document – Admin – (Jinqiu) – ***Dr. Cohen reports on day 2*** – Jinqiu has drafted an *N*-Nitrosation Resource Document for Panel review. The document examines the possible sources of nitrosamine impurities in cosmetic products, provides a concise overview of the existing regulatory framework governing the formation of nitrosamines in cosmetic ingredients and formulations, as well as conducts an in-depth analysis of the diverse factors that influence nitrosamine formation. Additionally, the document offers an extensive exposition of the Panel's considerations during the evaluation and determination process of potential risks linked to *N*-nitrosation in cosmetic formulations and applications.

The Panel is requested to review the draft resource document and assess the extent to which it concurs with their current perspective on the risks associated with *N*-nitroso compound formation during their review process of cosmetic ingredient safety. ***The Panel should determine how, and to what extent, the document should be revised.***

5. Draft 2024 Priorities - Amendment – Admin (Bart) – ***Dr. Belsito reports on day 2*** – The 2024 Draft Priority List was discussed by the Panel at their March 2023 meeting. Since the March meeting, CIR has received communications from members of the US FDA nominating ingredient additions to this priorities list, for-cause. Specifically, the FDA nominated Toluene and Dibutyl Phthalate for accelerated rereviews, and Trimethylbenzoyl Diphenylphosphine Oxide for 1st time review prioritization. The accelerated rereviews of Toluene and Dibutyl Phthalate have now been docketed.

   Trimethylbenzoyl Diphenylphosphine Oxide has not yet been assessed for safety by this Panel. Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (TPO; INCI name: Trimethylbenzoyl Diphenylphosphine Oxide; CAS No. 75980-60-8) is listed on Annex III in the EU, restricted to artificial nail systems at 5% in ready for use preparations, and only for professional use (as of May 22, 2019). On February 17, 2023, the ECHA launched a 45-day consultation for their plan for this ingredient to be added to the substances of very high concern (SVHC). Reportedly, there are new developmental and reproductive toxicity concerns. According to data received from the FDA VCRP earlier this year, this ingredient is reported to be used in 127 unique cosmetic formulations (FOU by category: Basecoats and Undercoats 9, Nail Extenders 1, Nail Polish and Enamel 106, Nail Polish and Enamel Removers 4, and Other Manicuring Preparations 7). ***Would the Panel like to add this ingredient to the 2024 Priorities List?***

6. Format & SOPs – Admin (Monice) – ***Dr. Belsito reports on day 2*** – At the September 2022 meeting, a document capturing standard language used in CIR reports, and the standard operating procedures (SOPs) used to develop that language, was provided for review. At that time, comments were made on several of the boilerplates. Accordingly, an update to those boilerplates is provided for review and comment.

   Additionally, over the last few meetings, there have been discussions regarding the wording of re-review summaries. Consequently, included herein, are templates proposed for use with re-review summaries for consideration and comment.

Full Panel Meeting

The Panel will consider the 3 reports to potentially be issued as final safety assessments, followed by the remaining reports advancing in the process (including the Tentative Reports and Draft Reports). In addition, a consensus should be reached for the 5 rereview documents, the 3 rereview summaries, and the 3 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 ***in-person***!

Agenda
165th Meeting of the Expert Panel for Cosmetic Ingredient Safety
June 12th – 13th, 2023

Monday, June 12, 2023

8:30 AM **WELCOME TO THE 165th EXPERT PANEL TEAM MEETINGS** **Drs. Bergfeld/Heldreth**

8:45 AM **TEAM MEETINGS** **Drs. Belsito/Cohen**

	Dr. Belsito's Team		**Dr. Cohen's Team***
FR (PC)	Hyaluronates	FR (RT)	Phytosteryl Glutamates
DR (PC)	Prostaglandins	TR (RT)	*Zanthoxylum piperitum*
DR (PC)	Amphocarboxylates	DAR (RT)	MIBK
RevDR (PC)	Yeast	RR (RT)	Polyquaternium-11
FAR (CB)	5-Amino-6-Chloro-*o*-Cresol	TR (PR)	Phenyl-Substituted Methicones
TAR (CB)	6-Amino-*m*-Cresol	DR (PR)	Polyglycerins
TAR (CB)	6-Amino-*o*-Cresol	RR (PR)	BHA
TR (CB)	Olive	RR (PR)	Octoxynols
RR (CB)	Lanolin	RR (PR)	Benzaldehyde
RRsum (MF|BH)	RR Summaries (all)	RRsum (BH|MF)	RR Summaries (all)
Admin (BH|MF)	Priorities	Admin (BH|MF)	Priorities
Admin (MF|BH)	Format & SOPs	Admin (MF|BH)	Format & SOPs
FR (RT)	Phytosteryl Glutamates	Admin (JZ)	Nitrosation
TR (RT)	*Zanthoxylum piperitum*	DR (PC)	Prostaglandins
DAR (RT)	MIBK	DR (PC)	Amphocarboxylates
RR (RT)	Polyquaternium-11	RevDR (PC)	Yeast
TR (PR)	Phenyl-Substituted Methicones	FR (PC)	Hyaluronates
DR (PR)	Polyglycerins	FAR (CB)	5-Amino-6-Chloro-*o*-Cresol
RR (PR)	BHA	TAR (CB)	6-Amino-*m*-Cresol
RR (PR)	Octoxynols	TAR (CB)	6-Amino-*o*-Cresol
RR (PR)	Benzaldehyde	TR (CB)	Olive
Admin (JZ)	Nitrosation	RR (CB)	Lanolin

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

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

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

*Team moves to the breakout room.

Tuesday, June 13, 2023			
8:30 AM	**WELCOME TO THE 165th FULL EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:40 AM	Admin	**MINUTES OF THE MARCH 2023 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		
	FAR (CB)	5-Amino-6-Chloro-*o*-Cresol – ***Dr. Cohen reports***	
	FR (RT)	Phytosteryl Glutamates – ***Dr. Belsito reports***	
	FR (PC)	Hyaluronates – ***Dr. Cohen reports***	
	Reports Advancing		
	DR (PC)	Prostaglandin Analogues – ***Dr. Belsito reports***	
	RevDR (PC)	Yeast – ***Dr. Cohen reports***	
	DR (PC)	Fatty Amphocarboxylates – ***Dr. Belsito reports***	
	DAR (RT)	MIBK – ***Dr. Cohen reports***	
	TR (RT)	*Zanthoxylum piperitum*-derived ingredients – ***Dr. Belsito reports***	
	DR (PR)	Polyglycerins – ***Dr. Cohen reports***	
	TR (PR)	Phenyl-Substituted Methicones – ***Dr. Belsito reports***	
	TAR (CB)	6-Amino-*o*-Cresol – ***Dr. Cohen reports***	
	TAR (CB)	6-Amino-*m*-Cresol – ***Dr. Belsito reports***	
	TR (CB)	Olive - *Olea europaea*-derived ingredients – ***Dr. Cohen reports***	
	Other Items		
	RR (CB)	Lanolin – ***Dr. Belsito reports***	
	RR (RT)	Polyquaternium-11– ***Dr. Cohen reports***	
	RR (PR)	BHA – ***Dr. Belsito reports***	
	RR (PR)	Octoxynols – ***Dr. Cohen reports***	
	RR (PR)	Benzaldehyde – ***Dr. Belsito reports***	
	RRsum (PR|BH|MF)	Wild Yam - Dioscorea Villosa (Wild Yam) Root Extract – ***Dr. Cohen reports***	
	RRsum (PR|BH|MF)	Polyamino Sugar Condensate – ***Dr. Belsito reports***	
	RRsum (CB|BH|MF)	Sweet Almond - Prunus Amygdalus Dulcis (Sweet Almond) Seed Meal – ***Dr. Cohen reports***	
	Admin (MF)	Format & SOPs – ***Dr. Belsito reports***	
	Admin (JZ)	Nitrosation Resource Document – ***Dr. Cohen reports***	
	Admin (BH)	Priorities (Request) – ***Dr. Belsito reports***	

ADJOURN – *The next will be held in-person on **September 11 – 12, 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 || Rev: Revised || 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-FOURTH MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

March 6-7, 2023

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.

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

Linda Katz, M.D., M.P.H.

Prashiela Manga, 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, 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

Name	*Organization*
Nosheen Ahmad	Mary Kay, Inc.
Jay Ansell	Personal Care Products Council
Don Bjerke	Procter & Gamble
Liwen Chen	US FDA
Vivek Dadhania	Bath & Body Works
Silvia Pérez Damonte	CLAIM
Wendy Koch	SEHSE
Carol Eisenmann	Personal Care Products Council
Linda Giles	Transcription, Etc.
Courtney Griffin	Consumer Federation of America
Tracy Guerrero	SEHSC
Angela Cruz Hernandez	unidentified
Drew Kurtzman	unidentified
Thomas Myers	Personal Care Products Council
Lauren Nardella	The Rose Sheet
Kimberly Norman	Personal Care Products Council
Indira Oropeza	MANE Argentina
Kathy Plotzke	Dow
Karin Ross	Personal Care Products Council
Jannavi Srinivasan	US FDA
Teresa Washington	unidentified
Hong Xie	US FDA
Merle Zimmermann	American Herbal Products Association

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 164th meeting of the Expert Panel for Cosmetic Ingredient Safety. The Panel meeting would include speakers from the Personal Care Products Council on the new Modernization of Cosmetics Regulation Act of 2022 and review of twelve reports including seven final reports, one tentative report, four draft reports, six re-reviews, and five re-review summaries. The Panel would also review the draft 2024 priorities and a resource document on hair dye epidemiology.

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 asked Ms. Monice Fiume to discuss the new use table format. Ms. Fiume described how the tables are arranged to summarize number of cosmetic uses and the concentration of use data by exposure type and by product category, which is a hybrid of the two use table formats that have been used by CIR staff in the past.

APPROVAL OF MINUTES

The minutes of the December 5-6, 2022 (163rd) Expert Panel meeting were approved. Discussion on an editorial comment was made on Basic Yellow 87.

DIRECTOR'S REPORT

Dr. Heldreth honored the memory of CIR's beloved past Director, Dr. F. Alan Andersen. Alan joined the US FDA in 1971, where he worked until becoming the Director of CIR in 1993. Alan then led CIR for 20 years, retiring in 2013. Throughout his career, Alan was a champion for public health, and he 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.

Dr. Heldreth also reiterated his gratitude to each and every one of the Panel members and liaisons, and the CIR staff, for all their hard work.

FINAL SAFETY ASSESSMENTS

Basic Yellow 87

The Panel issued a Final 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.

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 reviewed 2023 FDA VCRP data and noted that Basic Yellow 87 is still reported to be used in 5 non-coloring cosmetic products (i.e., 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 use is 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 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 Final Report 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/Leaf/Stem Extract
Malva Sylvestris (Mallow) Flower	Malva Sylvestris (Mallow) Leaf Extract
Malva Sylvestris (Mallow) Flower Extract	Malva Sylvestris (Mallow) Leaf Powder
Malva Sylvestris (Mallow) Flower/Leaf Extract	Malva Sylvestris (Mallow) Oil*

**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.*

The Panel reviewed 2023 FDA VCRP data and did not consider changes in the reported use of these ingredients to be significant. The Panel noted the reported use of some of these ingredients in products that are applied near the eye, and the lack of ocular irritation data. However, the Panel

reasoned that mallow constituents were non-irritating on the skin and such cosmetic formulations are not intended for direct instillation in the eye so that any ocular exposure would be incidental. Additionally, the *Malva sylvestris* (mallow)-derived ingredients are reported to be used at low concentrations in cosmetic formulations. Furthermore, Malva Sylvestris (Mallow) Flower/Leaf/Stem Extract and Malva Sylvestris (Mallow) Flower Extract were not sensitizing, and confirmed food use mitigated systemic toxicity concerns and supported the safety of these ingredients. However, because final product formulations may contain multiple botanicals, each containing the same constituents of concern, formulators are advised to be aware of these constituents to avoid reaching levels that may be hazardous to consumers; with *Malva sylvestris* (mallow)-derived ingredients, the Panel was concerned about the presence of potential sensitizers (e.g., cinnamal) in cosmetics.

Naturally-Sourced Clays

The Panel issued a Final 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 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*	Fuller's Earth*	Illite
Bentonite*	Hectorite*	Montmorillonite*
Clay		

**Previously reviewed by the Panel.*

The Panel reviewed 2023 FDA VCRP data and determined that the product categories and number of uses for these ingredients were similar to those reported in 2022.

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 would limit exposure, and processing would be expected to result in much larger particle sizes (by, for example, agglomeration) in the consumer product.

Octyldodecyl Stearoyl Stearate

The Panel issued a Final Amended Report 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 reviewed 2023 FDA VCRP data and determined that the product categories and number of uses for these ingredients were similar to those reported in 2022.

The Panel noted that development and reproductive toxicity (DART) data and carcinogenicity data are absent. However, the need for DART studies was mitigated because absorption is expected to be minimal, and a 14-d oral toxicity study did not suggest this ingredient was systemically toxic. Furthermore, the need for carcinogenicity data was mitigated by negative genotoxicity studies. A formulation containing 21% Octyldodecyl Stearoyl Stearate was not a sensitizer in a human repeated-insult patch test. However, the Panel was concerned that the potential exists for ocular irritation with the use of products formulated with Octyldodecyl Stearoyl Stearate. Accordingly, the Panel specified that products containing Octyldodecyl Stearoyl Stearate must be formulated to be non-irritating.

Polyhydroxystearic Acid

The Panel issued a Final Report with the conclusion that the following 3 ingredients are safe as used 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.*

The Panel reviewed 2023 FDA VCRP data and did not consider changes in the reported use of these ingredients to be significant. The Panel relied upon the large molecular weights of these ingredients (precluding absorption), prior safety assessments of the corresponding monomers of these ingredients, and safety of these ingredients as seen in 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 to support the systemic safety of these ingredients. Furthermore, negative dermal irritation and sensitization data included in this review reassured the Panel of the dermal safety of these ingredients.

***Rosa centifolia* – Derived Ingredients**

The Panel issued a Final Report 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 this 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*

**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.*

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 Panel reviewed 2023 FDA VCRP data and determined that the product categories and number of uses for these ingredients were similar to those reported in 2022. Additionally, the Panel discussed studies by the Research Institute for Fragrance Materials (RIFM) that reported Rosa Centifolia Flower Extract being evaluated at 2%, and not undiluted as currently stated in the report; this did not change the opinion of the Expert Panel. However, because final product formulations may contain multiple botanicals, each containing the same constituents of concern, formulators are advised to be aware of these constituents to avoid reaching levels that may be hazardous to consumers; with *Rosa centifolia*-derived ingredients, the Panel was concerned about the presence of citronellol and geraniol, which could result in sensitization reactions.

For the 3 *Rosa centifolia*- derived ingredients for which the Panel determined the data were insufficient, the Panel felt that there may be differences in the methods of manufacturing, compositions and impurities, and other data points, as compared to the ingredients that had sufficient data. Thus, it was unclear if inferences from the flower, bud and stem could be applied to the callus culture, leaf cell, and whole plant extract. Accordingly, the additional data needed to determine the safety of these ingredients in cosmetics 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 at expected maximum concentration of use

Trisodium Ethylenediamine Disuccinate

The Panel issued a Final Report with the conclusion that Trisodium Ethylenediamine Disuccinate and Tetrasodium Iminodisuccinate are safe as used in the present practices of use and concentration as described in the safety assessment. The Panel reviewed 2023 FDA VCRP data and determined that the product categories and number of uses for these ingredients were similar to those reported in 2022.

The safety of these ingredients is supported by available impurities, systemic toxicity, dermal irritation and sensitization, and ocular irritation data. The Panel noted mutagenicity in an in 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, and several other in vitro and in vivo genotoxicity assays had negative results. In addition, the Panel noted reproductive toxicity observed in assays performed in rats orally administered Trisodium Ethylenediamine Disuccinate; the Panel determined that these effects would not be relevant to cosmetic exposure due to the high doses/concentrations used in these studies.

TENTATIVE SAFETY ASSESSMENTS

5-Amino-6-Chloro-*o*-Cresol

The Panel issued a Tentative Amended Report for public comment with the conclusion that 5-Amino-6-Chloro-*o*-Cresol is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment. This Panel previously reviewed this ingredient as part of a larger group of amino cresol hair dyes; however, because the Panel determined that data for these amino cresol hair dye ingredients could not be read-across the group, re-reviews of each hair dye included in that original 2004 report will now be presented as individual stand-alone reports.

5-Amino-6-Chloro-*o*-Cresol 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 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 the available toxicokinetic studies show that 5-Amino-6-Chloro-*o*-Cresol absorbs slowly through the skin, is not genotoxic, and has low 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 determine the safety of 5-Amino-6-Chloro-*o*-Cresol for use as a hair dye ingredient.

Hyaluronates

The Panel issued a Tentative Report for public comment with the conclusion that the following 7 hyaluronate ingredients are safe in the present practices of use and concentration:

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

Three of these ingredients (Hyaluronic Acid, Potassium Hyaluronate, and Sodium Hyaluronate) have been previously reviewed by the Panel and were considered safe in the present practices of use and concentration, as described in the 2009 safety assessment. Because these ingredients would soon be considered for re-review, the Panel deemed it appropriate to include the 3 previously-reviewed ingredients in this safety assessment. The report was precipitated by the frequency of use reported for Sodium Acetylated Hyaluronate and Hydrolyzed Hyaluronic Acid in 2022.

The Panel noted sensitization studies included in the report art not performed at maximum use concentrations. However, the Panel determined additional studies are not needed to determine the safety of this ingredient group because these ingredients have large molecular weights (and as such are not expected to absorb into the skin) and because these ingredients are widely utilized and there is lack of case reports following topical applications. The Panel did note case reports of hypersensitivity reactions following use of Hyaluronic Acid dermal fillers, but stated these effects would not be relevant to cosmetic safety as dermal fillers are administered via intradermal injection and therefore bypass the stratum corneum. Concern was further mitigated as the majority of Hyaluronic Acid fillers contain cross-linked hyaluronates, which chemically differ from the non-cross-linked ingredients reviewed in this report.

Safety of these ingredients was supported by available toxicity data, the presence of Hyaluronic Acid as an endogenous substance in the skin, and the extensive use of these ingredients without reported adverse effects. In addition, the Panel noted that these ingredients may be derived from biological sources (i.e., rooster combs) and thus, manufacturers should take caution when formulating these ingredients to ensure that impurities (e.g., nucleic acids, proteins, endotoxins), detectible pathogenic viruses or infectious agents, and heavy metals would not be present in the final formulation.

INSUFFICIENT DATA ANNOUNCEMENTS

5-Amino-4-Chloro-*o*-Cresol

The Panel issued an Insufficient Data Announcement (IDA) for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl. The additional data needed to determine safety for these hair dyes are:

- Method of manufacturing
- Concentration of use

Basic Blue 99

The Panel issued an IDA for Basic Blue 99. The additional data needed to determine safety for this hair dye ingredient are:

- Method of manufacturing
- Composition and impurities data
    - Depending on the results of these data, additional information on toxicological endpoints may be needed

Phenyl-Substituted Methicones

The Panel issued a second 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 Panel received a data submission from the Silicones, Environmental, Health, and Safety Center (SEHSC). As part of that submission, data were submitted for Phenyl Trimethicone, based on the CAS number (70131-69-0, which according to the wINCI *Dictionary* is one of the CAS numbers for Phenyl Trimethicone). However, the test article was referred to as phenyl silsesquioxanes, or simply as the generic terms test material or test substance. It is unclear to the Panel as to whether any of those submitted data actually refer to Phenyl Trimethicone, and if they are applicable to this safety assessment. The Panel noted that phenyl silsesquioxanes is not a cosmetic ingredient and it has a cage-like structure, whereas the phenyl-substituted methicones are linear. In particular, the Panel noted an acute inhalation toxicity study in which rats were exposed whole body to an aerosol of 0.5 and 5 mg/l phenyl silsesquioxanes for 4 h, and the resulting LC_{50} was 0.5 mg/l.

Accordingly, the Panel determined the following are needed:

- Clarification of the identity and chemical nomenclature for test substances referred to in the SEHSC data submission
- Applicability of these data for use in this assessment
- Additional respiratory toxicity data at, or above, the reported maximum concentration of use in inhaled exposures near the face (Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    - Preferably, the protocol should be similar to the short-term inhalation study of rats exposed to an aerosol containing 3% Phenyl Trimethicone that is described in the original report (30-s burst, followed by a 15-min exposure within a chamber)

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

- MIBK – 1 ingredient
- Propylene Carbonate – 1 ingredient
- Stearalkonium Chloride – 1 ingredient (additional previously unreviewed ingredients will be added)

In contrast, the Panel reaffirmed the conclusions reached for the following 3 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.

- Dioscorea Villosa (Wild Yam) Root Extract – 1 ingredient
- Polyamino Sugar Condensate – 1 ingredient
- Prunus Amygdalus Dulcis (Sweet Almond) Seed Meal – 1 ingredient

RE-REVIEW SUMMARIES

Once the Panel determines to not reopen a previously-issued safety assessment, thereby reaffirming the existing conclusion, a re-review summary is prepared. The Panel approved the following 5 re-review summaries:

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

2024 Draft Priorities

The CIR Procedures require preparation of the 2024 Draft Priority List for public comment by June 1, 2023. However, it is advantageous for the 2024 Draft Priority List to be issued for public comment earlier (March 2023) in the process to allow more time for the acquisition of data. The priority list is typically based on stakeholder requests (e.g., a hair dye) and frequency of use (FOU) data from FDA's VCRP; this year, VCRP data were received from the FDA on February 2 (in response to a Freedom of Information Act request). In addition to a hair dye that will be provided by the PCPC Hair Coloring Technical Committee (HCTC), a few other ingredients are included for cause as proposed by various stakeholders.

While the list below includes only the lead ingredients, groupings of ingredients, drafted by CIR Staff, can be found in the Panel meeting book (https://www.cir-safety.org/sites/default/files/Admin_Priorities_1.pdf). There were 20 reports proposed, covering 40 ingredients, on the 2024 Draft Priorities List that was presented to the Panel. However, the Panel requested that the review of Propolis Extract be accelerated. Accordingly, this ingredient group has been added to the 2023 Priority List, and the current list will be amended to reflect this change. Additionally, 2 other ingredients that were initially proposed were removed from the list, and it was determined that Cannabidiol should be reviewed singly.

Once a proposal of a hair dye for assessment has been received from the HCTC, 18 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.

The proposed priorities for 2024 are:

2024 Draft Priorities List

Ingredient	Frequency of Use (FOU) Data Year: 2023
For cause	
***To be determined* - hair dye**	-
Cannabidiol	**32**
Basic Blue 7	**1**
Tetrabromophenol Blue	**2**
Per FOU	
Polyacrylate-13	**265**
Polygonum Cuspidatum Root Extract	**245**
Xylitylglucoside	**213**
Phytosphingosine	**210**
Sodium Hyaluronate Crosspolymer	**207**
Polyacrylate Crosspolymer-6	**205**
Trimethylpentanediyl Dibenzoate	**202**
Tosylamide/Epoxy Resin	**189**
Carnosine	**184**
Madecassoside	**182**
Sophora Flavescens Root Extract	**179**
Curcuma Longa (Turmeric) Root Extract	**177**
Lonicera Japonica (Japanese Honeysuckle) Flower Extract	**175**
Perfluorohexylethyl Triethoxysilane	**172**

Hair Dye Epidemiology Resource Document

The Panel reviewed the updated draft of the Hair Dye Epidemiology Resource Document, and considered the newly added studies to be well documented and noted that the re-organization of the tables meets their requirements on data interpretation and presentation (https://www.cir-safety.org/sites/default/files/Admin_HairDyeEpi.pdf). The Panel acknowledged the document continues to support the conclusion that the currently available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer. The Panel further suggested that, following a few editorial changes, the document be published in an appropriate epidemiology journal. This document will be brought before the Panel once more prior to finalization and submission to a journal.

Presentation – MoCRA

The Panel was briefed on the Modernization of Cosmetics Regulation Act of 2022 (MoCRA). Two speakers from PCPC, Thomas F. Myers (Executive Vice President, Legal & Regulatory Affairs) and Karin Ross (Executive Vice President, Government Affairs), provided the Panel with a very detailed and informative description of MoCRA.

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Memorandum

Date: March 19th, 2023

From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review

To: All Stakeholders

Re: 2024 Draft Priority List - Amendment

The 2024 Draft Priority List was discussed by the Panel at their March 2023 meeting. The draft priority list comprises nominated-for-cause ingredients and ingredients with the highest frequency of use (FOU) that have yet to be reviewed by the Panel. Since the March meeting, CIR has received communications from members of the US Food and Drug Administration (FDA) nominating ingredient additions to this priorities list, for-cause. Specifically, the FDA nominated Toluene and Dibutyl Phthalate for accelerated rereviews, and Trimethylbenzoyl Diphenylphosphine Oxide for 1st time review prioritization.

Toluene was previously assessed for safety by this Panel, as published in 1987, and determined to be safe for cosmetic use at the present practices of use and concentration. In 2006, the Panel reaffirmed this conclusion in a rereview summary. Since it has been at least 15 years since that last review of this ingredient, a CIR analyst is already working on the preparation of this rereview. Since this ingredient has been nominated-for-cause, CIR will present the Panel with a Draft Amended Report on this ingredient, instead of an abbreviated rereview document. According to data received from the FDA Voluntary Cosmetic Registration Program (VCRP) earlier this year, this ingredient is not reported to be in use.

Dibutyl Phthalate (along with Dimethyl Phthalate and Diethyl Phthalate) was previously assessed for safety by this Panel, as published in 1985, and determined to be safe for topical application in the present practices of use and concentration in cosmetics. In 2005 and 2017, the Panel reaffirmed this conclusion in rereview summaries (and added Butyl Benzyl Phthalate). Since Dibutyl Phthalate has been nominated-for-cause, CIR will present the Panel with a Draft Amended Report on Dibutyl Phthalate, Dimethyl Phthalate, Diethyl Phthalate, and Butyl Benzyl Phthalate, instead of an abbreviated rereview document. According to data received from the FDA VCRP earlier this year, of these 4 ingredients, only Diethyl Phthalate is reported to be in use (1 reported formulation).

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Trimethylbenzoyl Diphenylphosphine Oxide has not yet been assessed for safety by this Panel. Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (TPO; INCI name: Trimethylbenzoyl Diphenylphosphine Oxide; CAS No. 75980-60-8) is listed on Annex III in the EU, restricted to artificial nail systems at 5% in ready for use preparations, and only for professional use (as of May 22, 2019). On February 17, 2023, the European Chemicals Agency (ECHA) launched a 45-day consultation for their plan for this ingredient to be added to the substances of very high concern (SVHC). Reportedly, there are new developmental and reproductive toxicity concerns. According to data received from the FDA VCRP earlier this year, this ingredient is reported to be used in 127 unique cosmetic formulations (FOU by category: Basecoats and Undercoats 9, Nail Extenders 1, Nail Polish and Enamel 106, Nail Polish and Enamel Removers 4, and Other Manicuring Preparations 7). ***Would the Panel like to add this ingredient to the 2024 Priorities List?***

From: Manga, Prashiela
To: Bart Heldreth
Cc: Katz, Linda; Srinivasan, Jannavi
Subject: Ingredients for consideration at CIR
Date: Monday, March 20, 2023 11:21:55 AM

Dear Bart

FDA would like to propose the chemicals below for consideration to review/rereview. Is there a formal process for submitting requests, such as the need for an official letter from FDA?

Two have been reviewed previously but not recently, while diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (TPO) has been identified by ECHA as a "substance of very high concern".

Thank you
Prashiela

Dibutyl Phthalate:
Original review: 1985
Conclusion: Safe for topical application in the present practices of use and concentration in cosmetics.
Re-review Consideration: 2002 (Report published in 2005)
Conclusion: Not reopen, Reaffirmed the 1985 conclusion.
Re-review Consideration: 2012 (Report published in 2017)
Conclusion: Not reopen, Reaffirmed the 1985 conclusion.

Toluene:
Original review: 1987
Conclusion: Safe for topical application in the present practices of use and concentration in cosmetics.
Re-review Consideration: 2004/2005 (Report published in 2006)
Conclusion: Not reopen, Reaffirmed the 1987 conclusion.

Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (TPO)
No review record.