ADMIN

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Minutes

EXPERT PANEL MEETING
December 4-5, 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: 167th Meeting of the Expert Panel — Monday and Tuesday, December 4th - 5th, 2023
Date: November 9th, 2023

Welcome to the final Panel Meeting of 2023! The agenda and accompanying materials for the 167th Expert Panel Meeting, to be held on December 4th – 5th, 2023, are now available. ***The location is different from our meeting in September*** – this meeting will be held virtually via the Microsoft Teams platform. Additionally, ***the start time is new; both days will start at 9:30 AM EST***, for the benefit of our colleagues in the west. Invitations (3) to join the meeting will arrive separately in your email inbox. Panel members and liaisons will be registered automatically. However, other interested parties may register to attend in advance of the meeting at the meeting page:

https://www.cir-safety.org/meeting/167th-expert-panel-meeting

The meeting agenda includes the consideration of 8 reports advancing in the review process, including 2 final reports, 3 tentative reports, and 3 draft reports. Also on the agenda, are 6 rereview documents (2 proposals for rereview and 4 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.*** In addition to the rereview summaries, there are 3 other administrative documents, including a Resource Document regarding Nitrosation, a Resource Document regarding Inhalation, and a draft set of *in silico* Tools for the Panel's consideration.

Just as a reminder, while CIR was able to obtain updated frequency of use (FOU) 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 which is not yet open for submissions. The deadline for this new reporting program, *Cosmetics Direct*, which was originally set to be mandatorily reported into by the end of this year, has been extended for 6 months. Accordingly, CIR will continue to utilize the FOU data received this year from the VCRP until *Cosmetics Direct* is fully populated.

Also, in an attempt to reduce the quantity of late breaking information, we are making a cutoff for nearly all information sent to the Panel. The exception to this cutoff is any pertinent information relevant to a Draft Final Report. ***Submissions received on non-final reports, after the issuance of the Wave 2 supplement on November 20th, will be held back until the next iterations of those reports (e.g., a submission received on November 21st for the draft amended Octoxynols report would not be forwarded to the Panel until the next iteration is reviewed at a future meeting).***

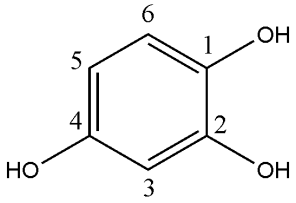
Finally, we have two sets of presentations scheduled. First, Dr. AJ Cuevas, Combe Sr. Manager Global Product Safety, has agreed to deliver a presentation regarding the dossier of information submitted by her company, titled "1,2,4-THB – Comprehensive Review of Chemical & Toxicological Data." Following, Mr. Craig Weiss, President CPTC, Mr. David Abramovitz, Partner Locke Lord, and Dr. Thomas Petry, Managing Director ToxMinds BVBA, will present on studies in support of Prostaglandins.



Team Meetings

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

1. 1,2,4-Trihydroxybenzene – DR (Christina) – ***Dr. Cohen reports on day 2*** – This is the first time the Expert Panel for Cosmetic Ingredient Safety (Panel) has seen a safety assessment of 1,2,4-Trihydroxybenzene as Used in Cosmetics. The Scientific Literature Review (SLR) was issued by CIR on September 28, 2023. This ingredient is reported to function as a hair colorant in cosmetic formulations. It is an auto-oxidative dye used in permanent hair dye formulations and gradual hair coloring shampoos and does not require hydrogen peroxide to activate oxidation and subsequent coupling reactions. Dr. AJ Cuevas of Combe is scheduled to present on this ingredient on day 1 of this meeting.

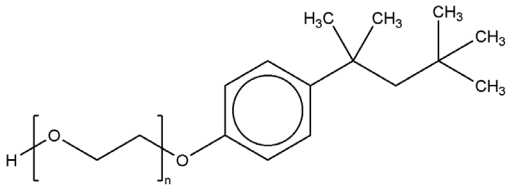


According to 2023 VCRP survey data, 1,2,4-Trihydroxybenzene is reported to be used in 18 hair dye formulations and 1 hair shampoo (coloring). The results of the concentration of use survey conducted by the Council indicate 1,2,4-Trihydroxybenzene is used at up to 2.5% in hair dyes and colors.

Jinqiu has performed a margin of safety (MOS) calculation for this ingredient, which has been summarized in the report. We consider this a draft calculation that the Panel should confirm or edit. Additionally, a supplier has provided an in vivo mammalian erythrocyte micronucleus assay in mice, a toxicological review, analyses, and a table of references from a literature review performed by their company. The micronucleus assay has been included within the genotoxicity section of the report. Upon review, the Panel should provide comments and discussion where needed.

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. Octoxynols – DAR (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel first published a final report on these 25 ingredients in 2004, with the conclusion that based on the animal and clinical data included in the report, 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. At its June 2023 meeting, the Panel decided to reopen this safety assessment to explore the mucous membrane irritation potential of these ingredients and newly reported use of Octoxynol-9 at 0.1% in other baby products.



Since the last review, reported frequencies and concentrations of use for these ingredients have decreased greatly. According to 2023 VCRP data, Octoxynol-11 is reported to have the greatest frequency of use, in 8 formulations; in 2021, it was reported to have 19 uses. In 2001, Octoxynol-9 was reported to be used in 131 formulations; however, according to 2023 VCRP data, it is only reported to now be used in 5 formulations. At the time of the original review, Octoxynol-10 had the greatest concentration of use, with a maximum concentration of use of 25% in hair lighteners with color; currently, no concentrations of use are reported for this ingredient. Results of the concentration of use survey conducted by the Council in 2022 indicate that Octoxynol-9 has the highest reported maximum concentration of use, at up to 2% in skin cleansing preparations; in 2001, Octoxynol 9 was reported to be used at up to 5% in cologne and toilet water formulations. The highest currently reported concentration of use resulting in leave-on dermal exposure is 1.5% Octoxynol-12 in face and neck preparations. Risk assessments for both 2% Octoxynol-9 in skin cleansing preparations and 1.5% Octoxynol-12 in face and neck preparations have been prepared by Dr. Zhu and are included in

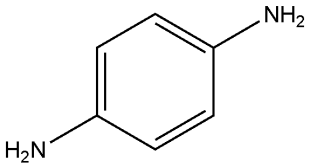
the report for the Panel's consideration.

The Panel has published reviews on the safety of nonoxynols in 1983, 1999, and 2015. In the original safety assessment of octoxynols, the Panel relied on the chemical similarity of these ingredients (1 carbon longer) to support the safety of octoxynols. Therefore, when data on octoxynols are absent, supporting data on nonoxynols has been included, as was done in the previous safety assessment of octoxynols; data from the 2015 final amended report on nonoxynols have also been included for potential read-across sources, as appropriate.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Amended 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.

3. *p*-Phenylenediamine – DAR (Christina) – ***Dr. Belsito reports on day 2*** – In 1985, the Panel published a safety assessment on *p*-Phenylenediamine with the conclusion that follows:

> *p*-Phenylenediamine is a known sensitizer, and some persons may be sensitized under intended conditions of use. For those persons not sensitized, the Expert Panel concludes that *p*-Phenylenediamine is safe as a hair dye ingredient at the current concentration of use.



This conclusion was reaffirmed in a re-review that was published by the Panel in 2006. In 2007, the Panel issued a Final Amended Report that included the dihydrochloride and sulfate salts (*p*-Phenylenediamine HCl and *p*-Phenylenediamine Sulfate). Because at least 15 years have passed since the Panel last reviewed this report, and many new references have been published on these ingredients, this amended safety assessment on *p*-Phenylenediamine, *p*-Phenylenediamine HCl, and *p*-Phenylenediamine Sulfate is being presented to the Panel in this Draft Amended Report.

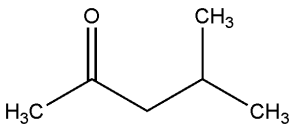
According to the 2023 VCRP survey data, *p*-Phenylenediamine is reported to be used in 200 formulations. The majority of these uses are in hair coloring preparations; however, uses have been reported for eye makeup preparations. Only 1 use was reported for *p*-Phenylenediamine HCl, in a hair coloring shampoo, and no uses were reported for the sulfate salt. The frequencies of use for *p*-Phenylenediamine have greatly decreased since the initial amended report was finalized; in 2007, *p*-Phenylenediamine was reported to have 1497 uses, all in hair coloring formulations. No uses were reported at that time for the related salts. The results of the concentration of use survey conducted by the Council in 2022 indicate *p*-Phenylenediamine has a maximum concentration of use range of 0.98 - 3% in hair dyes, with a maximum on-head concentration after dilution of 1%. No concentrations of use were reported for the related salts. In the 2007 amended report, the maximum concentration of use range for *p*-Phenylenediamine was 2 - 4% in hair dyes; the hydrochloride salt and the sulfate salt were each reported to be used at 6% in hair dyes.

This Draft Amended Report contains two MOS calculations performed by the SCCS. One is a conventional calculation, the other uses a toxicokinetic-based approach. ***Does the Panel agree with the calculations presented, or should a calculation be prepared by the Panel or CIR staff?***

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Amended 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.

Draft Tentative Reports - There are 3 draft tentative reports for consideration. - Issue a tentative conclusion?

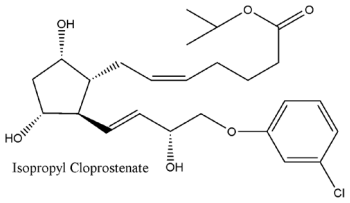
1. MIBK – TAR (Regina) – ***Dr. Belsito reports on day 2*** – In its initial assessment of MIBK that was published in 2004, the Panel concluded that based on the animal and clinical data included in the report, MIBK is safe as used in nail polish removers and as an alcohol denaturant in cosmetic products. In March 2023, the Panel re-opened the safety assessment of this ingredient. In its decision to reopen the assessment, the Panel considered new carcinogenicity and toxicology data provided by the National Toxicology Program (NTP); this study was in progress at the time of the original review of MIBK. After reviewing the Draft Amended Report at the June 2023 meeting, an IDA on MIBK was issued with the following data needs:

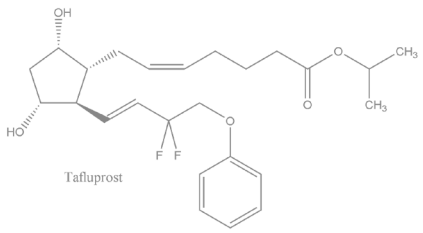


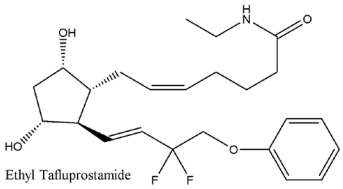
   - Concentration of use and function in aftershave formulations
   - Confirmatory sensitization studies at maximum use concentration

   No new data were received or found. A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider and 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 items for inclusion in the Discussion.

2. Prostaglandins – TR (Priya) – ***Dr. Cohen reports on day 2*** – At the June 2023 meeting, the Panel







   issued an IDA for these ingredients, and requested the following data:

   - concentration of use
   - information on packaging of products and directions for consumer use
   - 28-day dermal toxicity data; if absorbed, further systemic toxicological data may be needed
   - dermal sensitization and irritation data at maximum concentrations of use (if maximum concentrations of use are higher than the concentrations used in dermal irritation/sensitization studies already present in report)
   - intraocular pressure data on eyelash preparation containing Isopropyl Cloprostenate
   - potency/inhibition constant (Ki) binding affinity data on Ethyl Tafluprostamide and Isopropyl Cloprostenate as compared to bimatoprost (FDA-approved prostaglandin drug used for ocular hypertension/glaucoma treatment; also used as eyelash lengthener)

   Since the issuing of the IDA, a data supplement containing information on various endpoints and summaries of toxicity data on Ethyl Tafluprostamide has been provided. In addition to the summary document, full-length versions of many of these studies were also provided by the submitter and have been included herein. This data supplement also included information on a potentially related chemical, Tafluprost, along with the submitter's rationale for read-across justification. The numerous studies on Tafluprost are not summarized in the report at this time, awaiting input from the Panel as to whether data on Tafluprost is an appropriate read-across source to target either ingredient in this report. These data are summarized in an appendix.

   Furthermore, it should be noted that Tafluprost is a cosmetic ingredient listed in the *Dictionary*; however, no current uses are reported according to 2023 FDA VCRP data. ***The Panel should review the data on Tafluprost and determine whether these data are appropriate for addition in the current prostaglandin analogues report. If the Panel deems these data appropriate for addition, the Panel should determine whether these data should be added only as a read-across source, or, if Tafluprost be added to the report as an ingredient itself. (The safety***

assessment would then include Ethyl Tafluprostamide, Isopropyl Cloprostenate, and Tafluprost.) The majority of the systemic toxicity studies performed on Tafluprost used methods of administration that are not directly relevant to cosmetic exposure (e.g., intravenous injection). The Panel should take this into account when deciding if these data are appropriate for addition.

In addition to the data on Ethyl Tafluprostamide and Tafluprost, data on Isopropyl Cloprostenate were also submitted. These data include a summary of a use assay (subjects used eyelash serum containing 0.0044% Isopropyl Cloprostenate for 8 mo (evaluated irritation, pigmentation, periorbital volume loss)), a 28-d intraocular pressure assay, a safety assessment of Isopropyl Cloprostenate in eyelash serums, concentration of use data, and packaging/directions for consumer use.

It should be noted that the safety assessment of Isopropyl Cloprostenate provided in the submission includes systemic toxicity data on cloprostenol and travoprost (these are not cosmetic ingredients, according to the *Dictionary*). The data on cloprostenol and travoprost have not been incorporated into the report as the use of cloprostenol as a read-across source was previously rejected by the Panel. If these data are deemed appropriate by the Panel for inclusion in this report, they will be added prior to the next iteration.

All new data directly on Ethyl Tafluprostamide and Isopropyl Cloprostenate have been incorporated into the report and are indicated by highlighted text. A presentation is scheduled at this meeting on the topic of prostaglandins and may provide some insights for these and other data submitted.

No concentrations of use for Ethyl Tafluprostamide or Isopropyl Cloprostenate were submitted in response to the Council use survey performed in 2022. However, recently submitted data report that Isopropyl Cloprostenate is used in eyelash serums at up to 0.0075% (please note, these new data indicate a higher use concentration than what was previously reported), and Ethyl Tafluprostamide is used in products intended for eyelashes, eyebrows, or scalp hair at concentrations up to 0.02% (these data were included in the previous version of this report).

A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider and 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.

3. Yeast – TR (Priya) – ***Dr. Belsito reports on day 2*** – At the June 2023 meeting, the Panel reviewed the Revised Draft Report on these 56 yeast-derived ingredients and issued a second IDA for this ingredient group. (The first IDA was issued at the September 2021 meeting.) In this 2nd IDA, in order to determine the safety of these ingredients, the Panel requested confirmatory dermal sensitization data and data on food use/generally recognized as safe (GRAS) status on the yeast species used to derive these ingredients for all ingredients in which this is absent; in lieu of food use/GRAS status data, 28-d dermal toxicity data may be considered.

In addition, at the June meeting, the Panel requested information regarding Qualified Presumption of Safety (QPS) status (as designated by the European Union), in order to determine if this parameter may be used to clear the systemic toxicity/food use data needs for ingredients derived from yeast species that have a QPS status. Information on QPS status and a list of yeast species that have QPS status designation are included in this report package.

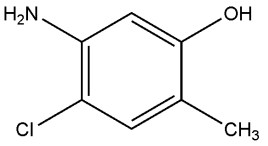
Since the issuing of the IDA, considerable additional information have been received. Accordingly, the data profile comprises 3 tables.

At the June 2023 meeting, the Panel questioned the removal of the following three yeast-derived ingredients: Hydrolyzed Yeast Protein, Yeast Beta-Glucan, and Yeast Polysaccharides. These ingredients were not included in the updated yeast-derived ingredient grouping, as they are discrete molecules. Historically, when the Panel has assessed the safety of natural complex substances (NCS), ingredients comprised of discrete molecules are typically excluded (e.g., rosmarinic acid was excluded from the review of rosemary-derived (NCS) ingredients).

A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider and 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 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. 5-Amino-4-Chloro-*o*-Cresol – FAR (Christina) – ***Dr. Cohen reports on day 2*** – At the September 2023 meeting, the Panel issued a Tentative Amended Report with the conclusion that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for these hair dye ingredients, the Panel was to conduct an MOS calculation based on the available data in this safety assessment, which has been completed. Herein, the SCCP MOS and a very conservative MOS performed by the Panel at the maximum reported use concentration are included in the report; both are considered protective.



   The Panel should carefully review the new MOS calculation, the Abstract, Discussion, and Conclusion, and issue a Final Amended Report.

2. Charcoal – FR (Christina) – ***Dr. Belsito reports on day 2*** – At the September 2023 meeting, the Panel concluded that Charcoal, Charcoal Extract, Charcoal Powder, and activated charcoal are safe in cosmetics in the present practice of use and concentration described in this safety assessment. Only plant-derived charcoal ingredients are included in this assessment; accordingly, charcoal derived from petroleum or other mineral sources are excluded from this review.

   Following the September meeting, the International Nomenclature Committee informed CIR staff that activated charcoal is a synonym of Charcoal Powder and is now described as such in the *Dictionary*. (An additional CAS No. associated with Charcoal Powder (64365-11-3) has also been added to this entry.) However, because activated charcoal is the more commonly known name in published literature and the medical community (and because some use data may have been reported under 1 name or both), it will be referred to as such herein in the appropriate studies but described under the ingredient heading Charcoal Powder.

   CIR staff noted a suggestion to mention D&C Black No. 2 in the Use section of this safety assessment. This colorant does not pertain to any of the ingredients in this report, thus it was not included in this section. The Introduction does inform the reader that colorants are not under the purview of the Panel and the use of such ingredients are not addressed in the safety assessment. No other unpublished data have been received for this report.

   Comments provided by the Council on the Tentative Report have been addressed. The Panel should carefully review the Abstract, Discussion, and Conclusion, and issue a Final Report.

Abbreviated Rereviews (i.e., rereview proposals) – There are 2 rereview documents – because it has at least been 15 years since the previous reviews were published, in accordance with CIR Procedures, in each case, the Panel is only being asked if the report should be reopened.

1. VA/Crotonates Copolymer – RR (Preethi) – ***Dr. Belsito reports on day 2*** – The Panel first published a review of the safety of VA/Crotonates Copolymer in 1983; at the time of the original review, this ingredient was named Vinyl Acetate/Crotonic Acid Copolymer. The Panel concluded that VA/Crotonates Copolymer is safe as a cosmetic ingredient under the present practices and concentration use, as described in that report. The Panel previously considered a rereview of this report in 2002 and re-affirmed the 1983 conclusion, as published in 2006.

   The Panel should consider whether the safety assessment of VA/Crotonates Copolymer should be reopened. In October 2023, an extensive search of the world's literature was performed for studies dated 2000 forward. No relevant published data were found. A historical overview, comparison of original and new use data, and the search strategy used are enclosed herein.

   During their previous review, the Panel had considered that although there were reports associating vinyl acetate with nasopharyngeal carcinoma in rat inhalation studies, it was demonstrated that carcinogenicity of vinyl acetate in rats is through a non-genotoxic mechanism, and the amount of residual vinyl acetate monomer in VA/Crotonates Copolymer was below the no-observed-effect level. Occupational studies confirmed no long-term effects in workers exposed to 5 to 10 ppm vinyl acetate, with intermittent exposures near 50 ppm and acute exposures to 300 ppm. Additionally, the Panel acknowledged the use of VA/Crotonates Copolymer in aerosol hair sprays, but stated that based on the particle size, VA/Crotonates Copolymer would not be respirable in formulation.

   Both the reported frequency of use and concentration of use for VA/Crotonates Copolymer have decreased since the last rereview. In 2002, 38 uses were reported, while 21 uses are reported in 2023. The maximum reported concentration of use in 2002 was 11% in hair sprays; the highest reported concentration of use in 2023 is 5.2% in a pump hair spray. Reported use categories have generally remained the same since the last review.

   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. Sodium Carbonates – RR (Regina) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate in 1987, with the conclusion that these ingredients are safe as presently used in cosmetic products, as described in that safety assessment. The Panel previously considered a rereview of this report and reaffirmed the 1987 conclusion, as published in 2006.

   The Panel should consider whether the safety of Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate should be reopened. In October 2023, an extensive search of the world's literature was performed for studies dated 2000 forward. A historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed herein.

   The frequency of use of Sodium Sesquicarbonate has decreased, while the frequencies of use for both Sodium Bicarbonate and Sodium Carbonate have increased since the previous rereview was conducted. Specifically, the frequency of use of Sodium Bicarbonate increased from 66 uses in 2002 to 571 reported uses in 2023. The maximum reported concentration of use of all 3 ingredients has decreased since the previous re-review.

   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.

Administrative Items - there are 4 rereview summaries (presented together in 1 "RRsums" book) and 3 other administrative items.

RRsums - The Panel is being asked for editorial comment.

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

2. Zinc Phenolsulfonate – RRsum – (Regina) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

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

4. Laneth-10 Acetate – RRsum – (Priya) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

Other Admin

5. Nitrosation Resource Document – Admin (Jinqiu) – ***Dr. Cohen reports on day 2*** – The Panel last reviewed this document at the June 2023 meeting, reaching a consensus on the need for further insights and edits from an outside expert conversant with the toxicity of *N*-nitroso compounds and related *N*-nitrosation pathways. In August 2023, the CIR Science and Support Committee (SSC) also reviewed and provided feedback on this draft document.

   Following the feedback received, the document has been substantially revised. Dr. Ronald C. Shank, who previously served as an esteemed member of the Expert Panel for Cosmetic Ingredient Safety and is a renowned expert on the topic of nitrosation and associated toxicities, dedicated his expertise to make the revisions.

   The Panel should review this Document and consider if it should be finalized to post on CIR's Findings & Resources Documents page (https://www.cir-safety.org/cir-findings). If the Document is not deemed fit for finalization, any specific requirements or modifications needed should be clearly indicated.

6. Inhalation Resource Document – Admin (Jinqiu) – ***Dr. Belsito reports on day 2*** – The Panel last approved this document at the December 2021 meeting. It has since been revised to incorporate new findings regarding the particle size distribution in certain propellant-based sprays, such as dry shampoos packaged in a powdered galenic formulation. A brief discussion on the categorization of dry shampoo products is also included.

   At the December 2021 meeting, the Panel discussed the potential inhalation risks resulting from aerosolized nano-enabled cosmetic products. The Panel re-emphasized that while particle/droplet size is crucial, other factors such as the physicochemical properties of ingredients in a spray formulation, systemic and local toxicity (e.g., effects on lung and skin), and realistic exposure scenarios under in-use conditions (considering parameters like spray product usage levels, ingredient concentrations, exposure duration and frequency, and the deposition of particles/droplets in human airway) also play significant roles in assessing the safety of inhaled ingredients from sprays. When spray parameters are insufficient to support a robust inhalation exposure assessment, the Panel would request additional information from Industry and further evaluate the sufficiency of other exposure and toxicity data on a case-by-case basis. The Panel concurred the CIR Resource Document – Respiratory Exposure to Cosmetic Ingredients would serve as a living document, continually integrating and adapting new findings pertinent to assessing the safety of ingredients through inhalation.

   The Panel should review the revised document and assess whether the updates have reflected their concerns with regard to particle size distribution and inhalation exposure parameters of spray applications that involve respirable fractions, as well as the specific considerations when accessing safety for ingredients that might be used in propellant-driven sprays and certain categories not well-defined in the current regulatory context. If these concerns are not adequately addressed, the Panel should determine how, and to what extent, the document should be further revised. Otherwise, the Panel should finalize this version to replace the current one posted on CIR's Findings & Resources Documents page (https://www.cir-safety.org/cir-findings).

7. Tools – Admin (Jinqiu) – ***Dr. Cohen reports on day 2*** – In response to the Panel's inquiry, the CIR SSC of the Personal Care Products Council shared a list of tools for literature exploration and toxicity evaluation. The submission made to the CIR included relevant published papers and user manuals; however, due to copyrights, only the memo providing the list of tools is included with this submission.

   Furthermore, the CIR SSC provided several review papers on new approach methodologies (NAMs) to support the "Next Generation Risk Assessment" (NGRA) for cosmetics ingredients and materials, including the application of machine learning and artificial intelligence approaches in toxicology, such as physiologically-based pharmacokinetic (PBPK) modeling, quantitative structure activity relationship (QSAR) modeling for toxicity prediction, adverse outcome pathway (AOP) analysis, etc.

   The submission features an article that introduces Vermeer Cosmolife, formerly known as SpheraCosmolife, which is a freely accessible software designed for the toxicological assessment of cosmetic ingredients. The software has been developed considering the regulatory framework for cosmetics. It may apply defined exposure scenarios, depending on product type, to derive risk for cosmetic consumers. This tool has already been used to calculate the MOS for ingredients, such as Octoxynols, and will be discussed in the draft report being reviewed at this meeting.

   In the submission, a review paper (Cronin et al. 2022) highlights prominent databases that may provide a broad selection of toxicological information and data for cosmetics-related materials. One example is the COSMOS NG (the public component of the ChemTunes·ToxGPS® web services). It has been proposed for use in read-across, as discussed at previous Panel meeting. Of note, COSMOS Threshold of Toxicological Concern (TTC) datasets played a pivotal role in the development of TTC specifically for cosmetics ingredients. This COSMOS approach led to the SCCS's most recent decision on the thresholds of 2.3 and 46 µg/kg bw/d for Cramer classes III and I, respectively, for use in relation to cosmetics-related substances.

   It is worth mentioning that some of the tools listed in the two documents are commercial. Their *in silico* predictions might be based on the provider's proprietary databases. Some companies have reservations about sharing complete analysis and prediction details. For instance, Lhasa Limited representatives assert that they cannot allow public access to Derek alerts and the full reports generated by Derek Nexus.

   The Panel is being asked to review the information provided in the submission, and consider the potential applications of the highlighted tools. Specially, the Panel should determine when results predicted by *in silico* approaches might be employed for assessing the safety of cosmetic ingredients.

Full Panel Meeting

The Panel will consider the 2 reports to potentially be issued as Final Reports, 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 2 rereview documents, the 4 rereview summaries, and the 3 other administrative items.

Please remember, the meeting starts at 9:30 AM on day 1 and day 2.

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

Agenda
167th Meeting of the Expert Panel for Cosmetic Ingredient Safety
December 4th – 5th, 2023

Monday, December 4, 2023

9:30 AM (EST)	**WELCOME TO THE 167th EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
9:45 AM	**PRESENTATION – 1,2,4-Trihydroxybenzene**	**Dr. AJ Cuevas (Combe)**
10:45 AM	**PRESENTATION – Prostaglandins**	**Mr. Weiss (CPTC), Mr. Abramovitz (Locke Lord), & Dr. Petry (ToxMinds BVBA)**
11:30 AM	**TEAM MEETINGS**	**Drs. Cohen/Belsito**

Dr. Cohen's Team*

DR (CB)	1,2,4-Trihydroxybenzene
DAR (CB)	*p*-Phenylenediamine
FAR (CB)	5-Amino-4-Chloro-*o*-Cresol
FR (CB)	Charcoal
RRsum (RT|MF|BH)	Isobutane
RRsum (PC|MF|BH)	Laneth-10 Acetate
RRsum (PC|MF|BH)	Sodium Dehydroacetate
RRsum (RT|MF|BH)	Zinc Phenolsulfonate
TAR (RT)	MIBK
RR (RT)	Sodium Carbonate
Admin (JZ)	Tools
Admin (JZ)	Inhalation Doc
Admin (JZ)	Nitrosation Doc
TR (PC)	Prostaglandins
TR (PC)	Yeast
DAR (PR)	Octoxynols
RR (PR)	VA/Crotonates Copolymer

Dr. Belsito's Team

TR (PC)	Prostaglandins
TR (PC)	Yeast
TAR (RT)	MIBK
RR (RT)	Sodium Carbonate
DAR (PR)	Octoxynols
RR (PR)	VA/Crotonates Copolymer
FAR (CB)	5-Amino-4-Chloro-*o*-Cresol
FR (CB)	Charcoal
DAR (CB)	*p*-Phenylenediamine
DR (CB)	1,2,4-Trihydroxybenzene
RRsum (RT|MF|BH)	Isobutane
RRsum (PC|MF|BH)	Laneth-10 Acetate
RRsum (PC|MF|BH)	Sodium Dehydroacetate
RRsum (RT|MF|BH)	Zinc Phenolsulfonate
Admin (JZ)	Nitrosation Doc
Admin (JZ)	Inhalation Doc
Admin (JZ)	Tools

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. For the virtual meeting, that is a separate Teams meeting room.

Tuesday, December 5, 2023			
9:30 AM (EST)	**WELCOME TO THE 167th FULL EXPERT PANEL MEETING**		**Dr. Bergfeld**
9:40 AM	Admin **MINUTES OF THE SEPTEMBER 2023 EXPERT PANEL MEETING**		**Dr. Bergfeld**
9:45 AM	**DIRECTOR'S REPORT**		**Dr. Heldreth**
10:00 AM	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**		
	Final Reports		
	FAR (CB)	5-Amino-4-Chloro-*o*-Cresol – ***Dr. Cohen reports***	
	FR (CB)	Charcoal ingredients – ***Dr. Belsito reports***	
	Reports Advancing		
	DR (CB)	1,2,4-Trihydroxybenzene – ***Dr. Cohen reports***	
	DAR (CB)	*p*-Phenylenediamine – ***Dr. Belsito reports***	
	TR (PC)	Prostaglandin Analogues – ***Dr. Cohen reports***	
	TR (PC)	Yeast ingredients – ***Dr. Belsito reports***	
	DAR (PR)	Octoxynols – ***Dr. Cohen reports***	
	TAR (RT)	MIBK – ***Dr. Belsito reports***	
	Other Items		
	RR (RT)	Sodium Carbonate – ***Dr. Cohen reports***	
	RR (PR)	VA/Crotonates Copolymer – ***Dr. Belsito reports***	
	RRsum (RT|BH|MF)	Zinc Phenolsulfonate – ***Dr. Cohen reports***	
	RRsum (RT|BH|MF)	Isobutane – ***Dr. Belsito reports***	
	RRsum (PC|BH|MF)	Laneth-10 Acetate – ***Dr. Cohen reports***	
	RRsum (PC|BH|MF)	Sodium Dehydroacetate – ***Dr. Belsito reports***	
	Admin (JZ)	Tools – ***Dr. Cohen reports***	
	Admin (JZ)	Inhalation Resource Document – ***Dr. Belsito reports***	
	Admin (JZ)	Nitrosation Resource Document – ***Dr. Cohen reports***	

ADJOURN – *The next will be held virtually on Thursday and Friday,* ***March 28 – 29, 2024****. 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-SIXTH MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

September 11-12, 2023

Melrose Hotel, 2430 Pennsylvania Ave, NW, Washington DC

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairperson

Donald V. Belsito, M.D., Teamleader

David E. Cohen, M.D., Teamleader

Curtis D. Klaassen, Ph.D.

Allan E. Rettie, Ph.D.

David Ross, Ph.D.

Thomas J. Slaga, Ph.D.

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

Susan Tilton, Ph.D.

Liaison Representatives

Consumer

Courtney Griffin, J.D.

Industry

Alex Kowcz, M.B.A.

Government

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

Jannavi Srinivasan, Ph.D.

Prashiela Manga, Ph.D.

Janet Zang, Ph.D.

_____

Adopted (Date)

_____

Wilma F. Bergfeld, M.D.

CIR Staff

Administration
Bart Heldreth, PhD - Executive Director

Monice Fiume, MBA - Senior Director

Carla Jackson - Administrative Coordinator

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

Analysis
Christina L. Burnett, MSES - Senior Scientific Analyst

Priya Cherian, MS - Senior Scientific Analyst

Preethi S. Raj, MS - Senior Scientific Analyst

Regina Tucker, MS –Scientific Analyst

Information Services
Kevin Stone Fries, MLS - Information Services Manager

Other Meeting Attendees

Name	*Organization*
Yunqi An (virtual)	Victoria's Secret
Valentine Anyaibe (virtual)	Enhanced Compliance, Inc.
Don Bjerke	Procter & Gamble
Leticia Peruffo Bueno (virtual)	unidentified
Marcos Cerquerira (virtual)	unidentified
Deborah Church (virtual)	Catalyst Clinical Research, LLC
Anne Corriou (virtual)	Givaudan
Andrea Arruda Costa (virtual)	Avon
Sara Eglitis (virtual)	Enhanced Compliance, Inc.
Carol Eisenmann	Personal Care Products Council
Dianne Eustice (virtual)	Givaudan
Arun Govindarajan (virtual)	unidentified
Jessie Gregson-Williams	Consumer Federation of America
Pertti Hakkinen (virtual)	NIH
Christopher-Tilman Krueger (virtual)	Beiersdorf
Jessica Madrigal (virtual)	unidentified
Kris Miles (virtual)	Nouryon
Nathaniel Minton (virtual)	Eastman Chemical Co.
Isabella Montuori (virtual)	Avon
Stefanie O'Neal (virtual)	Kao Corporation
Kamila Rzewucka (virtual)	Obelis Group
Alexandra Gorman Scranton (virtual)	Women's Voices for the Earth
Jose Flores Salgado (virtual)	unidentified
Carolina Santos (virtual)	unidentified
Daisy Shelton (virtual)	Eastman Chemical Co.
Brenda Shinyashiki (virtual)	Edgewell Personal Care
Alyne Simoes (virtual)	Natura & Co.
Marina Souza (virtual)	unidentified
Jannavi Srinivasan	US FDA
Liz Toledo (virtual)	unidentified
Brian Wall (virtual)	Colgate-Palmolive
Joseph Wang (virtual)	unidentified
Lauren Waters (virtual)	unidentified
Hong Xie	US FDA

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 166th meeting of the Expert Panel for Cosmetic Ingredient Safety. The Panel reviewed 9 documents, 6 re-reviews, and 2 re-review summaries. The Panel also reviewed 5 administrative documents, including the hair dye epidemiology resource document, FDA draft and SCCS notes of guidance documents, and final priorities list. Dr. Bergfeld acknowledged all the work put forth by the CIR staff and the Panel to prepare for this meeting.

Dr. Bergfeld noted the comments received from outside parties, including the Women's Voice for the Earth, on charcoal, phenyl-substituted methicones, and the toluene review. CIR staff have written responses to these comments.

Dr. Bergfeld expressed appreciation on behalf of the Panel that no late submissions of data were received. Dr. Bergfeld also acknowledged Dr. Bjerke and his presentation on skin sensitization risk assessment and new approach methodologies.

APPROVAL OF MINUTES

The minutes of the June 12-13, 2023 (165th) Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth thanked the members of and liaisons to the Expert Panel for Cosmetic Ingredient Safety, and noted that in addition to the 9 reports advancing in the review process, there was much discussion regarding numerous administrative items, with a collective eye to modernizing CIR and support for this Panel. The CIR Staff plans to investigate further modernization, including new methodologies, tools, and various notes of guidance to better support this Panel. Dr. Heldreth also thanked Dr. Bjerke for the timely and extremely relevant presentation, "Skin Sensitization Risk Assessment and Confidence in New Approach Methodologies".

In addition to presenting the great work of this Panel in June 2023 at the DGK/IKW: "Safety is the Key" - Scientific Conference on Safety Assessment (https://sicherheitsbewerter.info/veranstaltungsberichte/), Dr. Heldreth noted a reoccurring theme at the conference regarding these new methodologies and the importance of risk assessment in building confidence therein.

FINAL SAFETY ASSESSMENTS

6-Amino-*m*-Cresol

The Panel issued a Final Amended Report with the conclusion that the available data are insufficient to make a determination that 6-Amino-*m*-Cresol is safe under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for this hair dye, the following data are needed:

- Method of manufacture
- *in vivo* genotoxicity studies

The Panel determined that these data needs, from the original Insufficient Data Announcement (IDA) issued following the December 2022 Panel meeting, remain unmet. If these needs remain unmet after 2 years (September 15, 2025), this insufficient data conclusion will be transmuted to "Use Not Supported."

6-Amino-*o*-Cresol

The Panel issued a Final Amended Report with the conclusion that the available data are insufficient to make a determination that 6-Amino-*o*-Cresol is safe under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for this hair dye, the following additional data are needed:

- Method of manufacture
- Composition and impurities
- Concentration of use
- Absorption, distribution, metabolism, and excretion (ADME) studies
    - If absorbed, additional data (e.g., DART and genotoxicity data) may be needed

The Panel determined that these data needs, from the original IDA issued following the December 2022 Panel meeting, remain unmet. Since there are currently no reported uses of this ingredient, this insufficient data conclusion is immediately transmuted to "Insufficient Data–No Reported Use."

Olea europaea (Olive)-Derived Ingredients

The Panel issued a Final Report with the conclusion that the following 16 *Olea europaea* (olive)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Hydrolyzed Olive Fruit*
Hydrolyzed Olive Fruit Extract*
Hydrolyzed Olive Leaf Extract*
Olea Europaea (Olive) Fruit
Olea Europaea (Olive) Fruit Extract
Olea Europaea (Olive) Fruit Juice*
Olea Europaea (Olive) Fruit Juice Extract*
Olea Europaea (Olive) Fruit Unsaponifiables
Olea Europaea (Olive) Fruit Water*
Olea Europaea (Olive) Husk Powder*
Olea Europaea (Olive) Leaf*
Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Leaf Water

Olea Europaea (Olive) Seed*
Olea Europaea (Olive) Seed Powder

**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 that the available data are insufficient to make a determination that the following 7 *Olea europaea* (olive)-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Olea Europaea (Olive) Bark Extract**
Olea Europaea (Olive) Branch Extract**
Olea Europaea (Olive) Bud Extract
Olea Europaea (Olive) Flower Extract**
Olea Europaea (Olive) Flower Water**
Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Wood Extract**

***There are currently no uses reported for these ingredients. Accordingly, the conclusion for these ingredients is immediately transmuted to "Insufficient Data–No Reported Use."*

To come to a conclusion of safety for these 7 cosmetic ingredients, the following additional data are needed:

- Method of manufacture for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
- Composition and impurities data for Olea Europaea (Olive) Branch Extract and Olea Europaea (Olive) Flower Water
- 28-day dermal toxicity data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, 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 Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract

Polyglycerins

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 concentration described in the safety assessment:

Diglycerin
Polyglycerin-3
Polyglycerin-6
Polyglycerin-10

The Panel considered their prior safety determination of glycerin that was issued in 2019 and found it reasonable to use this information as supporting data for repeated dose oral toxicity, developmental and reproductive toxicity, and carcinogenicity endpoints. Additionally, the Panel discussed the otherwise robust toxicological profile, including negative dermal irritation and sensitization data, and that the negative log K_{ow} values for these ingredients (ranging from -8.6 to -2) would preclude absorption in the skin.

Linear Phenyl-Substituted Methicones

The Panel issued a Final Report for these 7 linear phenyl-substituted methicone ingredients and concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled:

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

The Panel considered a memorandum sent by the Silicones, Environmental, Health, and Safety Center (SEHSC) confirming that data submitted on Phenyl Trimethicone was actually on the material associated with CAS No. 70131-69-0 (i.e., polyphenylsilsesquioxane). Thus, the Panel agreed that these data are not appropriate for inclusion in the report. The Panel also discussed that because CAS No. 70131-69-0 initially had been erroneously associated with Phenyl Trimethicone, the reported frequencies and concentrations of use for Phenyl Trimethicone may be inflated.

The Panel agreed that data on short-term intermittent-exposure inhalation toxicity and on the particle size distribution and concentrations of use for these ingredients in products which may be incidentally inhaled are lacking. Thus, the Panel deemed the available data insufficient to make a determination of safety for these ingredients in products which could be incidentally inhaled.

***Zanthoxylum piperitum*–Derived Ingredients**

The Panel issued a Final Report with the conclusion that the following 4 *Zanthoxylum piperitum*-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:

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

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

The Panel noted that although there was a lack of general toxicity data, *Zanthoxylum piperitum* extract is classified as generally recognized as safe (GRAS) in foods, and its GRAS status mitigated toxicity concerns. Additionally, *Zanthoxylum piperitum*-derived ingredients have low reported maximum concentrations of use (i.e., 0.01%).

For *Zanthoxylum piperitum*-derived ingredients, the Panel was concerned about the presence of multiple terpene constituents (e.g., citronellol and geranyl acetate) in cosmetic ingredients, which could result in sensitization reactions. A human repeated-insult patch test (HRIPT) of a *Zanthoxylum piperitum* extract in ethanol at 2% deemed the test substance neither a sensitizer nor an irritant. However, 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. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

TENTATIVE SAFETY ASSESSMENTS

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

The Panel issued a Tentative Amended Report with the conclusion that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for these hair dye ingredients, the Panel will be conducting a margin of safety calculation based on the available data in this safety assessment. Once this calculation is performed and reviewed by the Panel at the next meeting, a final determination of safety will likely be made. No further data is requested at this time.

Plant-Derived Charcoal Ingredients

The Panel issued a Tentative Report for public comment with the conclusion that the following 4 plant-derived Charcoal ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Charcoal	Charcoal Powder
Charcoal Extract	Activated Charcoal *

**Not in the web-based International Cosmetic Ingredient Dictionary and Handbook (wINCI; Dictionary)*

Both the *Dictionary* and communications with the International Nomenclature Committee (INC) indicate that the source material for these cosmetic ingredients is plant-based, while carbon black (not an ingredient in this report) is sourced from minerals (e.g., petroleum). Clarification on the ingredient source for Activated Charcoal is being sought; however, the data in the report indicate it is also sourced from plants (e.g., bamboo). Carbon black and ingredients derived from mineral sources are not produced in the same manner (e.g., sourced from petroleum instead of plants) and are likely to have different compositions and impurities. The data in the report are specific to the plant-based materials and do not include carbon black.

The Panel discussed the issue of incidental inhalation exposure that may occur from the use of these ingredients in cosmetic formulations (i.e., Charcoal Powder is used in a hair spray at 0.001%). Limited data available from inhalation studies, including an acute rat study with Charcoal and an intratracheal rat carcinogenicity study with Charcoal Powder, suggest little potential for respiratory effects at relevant doses. The Panel considered other data available to characterize the potential for plant-derived Charcoal ingredients to cause systemic toxicity, irritation, sensitization, and genotoxicity. They noted the lack of systemic toxicity in acute and repeated dose studies at up to 11,240 mg/kg bw, a lack of irritation and sensitization in tests of dermal exposure, and the absence of genotoxicity in *in vitro* and *in vivo* test systems. Thus, based on all these findings, the Panel determined that plant-derived Charcoal ingredients are safe as used in cosmetics in the present practices of use and concentration described in the safety assessment.

INSUFFICIENT DATA ANNOUNCEMENTS

Pentapeptides

The Panel issued an insufficient data announcement for Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4. The additional data needed to determine the safety of these ingredients are:

- Dermal irritation and sensitization data for the lysine-threonine-serine-lysine-serine (KTSKS) amino acid sequence
- Skin penetration and degradation data for Myristoyl Pentapeptide-4 (KTSKS sequence)
- Clarification of the concentration of use tested in the HRIPT study currently summarized in the report on Palmitoyl Pentapeptide-4 (Pal-lysine-threonine-threonine-lysine-serine; Pal-KTTKS) sequence

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

- *Acacia senegal*-Derived Ingredients – 2 ingredients
- *t*-Butyl Alcohol – 1 ingredient

In contrast, the Panel reaffirmed the conclusions reached for the following 4 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.

- Isobutane, Isopentane, Butane, and Propane – 4 ingredients
- Laneth-9 Acetate and Laneth-10 Acetate – 2 ingredients
- Sodium Dehydroacetate and Dehydroacetic Acid – 2 ingredients
- Zinc Phenolsulfonate – 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 2 re-review summaries:

- Benzaldehyde – 1 ingredient
- Polyquaternium-11 – 1 ingredient

2024 FINAL PRIORITIES

There are 18 reports planned, covering 31 ingredients, on the 2024 Final Priorities List. While the priority list below includes only the lead ingredients, groupings of ingredients can be found on the CIR website. 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/ingredients to be assessed in 2024. Interested parties are encouraged to submit pertinent data to the CIR, as soon as possible, for use in the development of the Scientific Literature Reviews (SLR) for these ingredients. Although the specific data needs vary for each safety assessment, the following are typical data that the Panel reviews for each safety assessment.

- Chemistry, impurities, and method of manufacture
- Risk (e.g., margins of safety)
- Toxicokinetics data, specifically dermal absorption and/or penetration
- Repeated-dose toxicity data
- Inhalation toxicity data, if the ingredient is used in a product that can be incidentally inhaled
- Reproductive/developmental toxicity data
- Genotoxicity data; if positive, carcinogenicity data may be needed
- Dermal irritation and sensitization data at maximum concentration of use

For the review of botanical ingredients (natural complex substances (NCS)), the additional data needed include: species, plant part, extraction method, solvent, and data on component chemical characterization. It is important that these data are specific for the ingredient(s) as used in cosmetics.

2024 Final Priorities List

Ingredient	Frequency of Use (FOU) Data Year: 2023
For cause	
Cannabidiol	32
Basic Blue 7	1
Trimethylbenzoyl Diphenylphosphine Oxide	127
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**

NITROSATION RESOURCE DOCUMENT

The Panel discussed the FDA's guidance for industry regarding the recommended acceptable intake limits for nitrosamine drug substance-related impurities (NDSRIs). The Panel deliberated on the potential utilization of the approach, as proposed in the guidance document, to predict and categorize the carcinogenic potency of nitrosamine impurities in evaluating the safety of cosmetic products. The Panel noted the distinctions in usage scenarios between cosmetics and orally administered drugs should be considered, with special discussion on elements such as formulation, levels of exposure, rates

of absorption, and so forth. The Panel concurred that the guidance document should be cited in CIR's nitrosation resource document, which is currently being prepared, integrating pertinent and valuable information.

TOLUENE STRATEGY

A Final Report on Toluene was first published in 1987, with a conclusion of safe in the present practices of use and concentration, as described in that report. This conclusion was re-affirmed in a re-review published in 2006. In March 2023, Toluene was nominated for the 2024 Priority List by the FDA, and in June 2023, the Panel agreed to accelerate the re-review of this ingredient. Following this request, a literature search was performed on Toluene for studies dated 1983 forward, and a vast number of studies were found on many toxicological endpoints and effects related to human health. Due to the volume of literature found, at the September 2023 meeting, CIR staff presented a strategy memo to the Panel requesting guidance on what information should be included in the future Draft Amended Report. The Panel agreed to include studies published after 2005, excluding studies associated with high exposures and studies assessing repetitive occupational exposures. In addition to the Draft Amended Report, abstracts and citations of the studies not included in that report will be presented to the Panel for assessment for potential inclusion. In addition, the Panel noted that all governmental regulatory guidelines (e.g., National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit of 100 ppm (10 h time-weighted exposure); 150 ppm (short term exposure limit)) should be included in the report, along with a margin of safety calculation, similar to the calculation performed by the Danish Environmental Protection Agency (EPA) on formaldehyde. (For a more cautious exposure estimate, calculation should account for exposure to 20 nails, instead of 10 as used by the Danish EPA.)

DERMAL DOSE AND PRESENTATION

The Panel deliberated on the dose metrics used in the HRIPT. The Panel noted dose per unit area of skin is one of the important factors in interpretation of existing HRIPT data, which can be further employed to derive a No Expected Sensitization Induction Level (NESIL) using the QRA2 (Skin Sensitization Quantitative Risk Assessment 2) approach, in consideration of accumulative exposure of diverse cosmetic products that might be used consistently over prolonged durations. To ensure safety, the Panel intends to evaluate the concentration of the test substance in an HRIPT, expressed as dose per skin unit area; additionally, on a case-by-case basis, the Panel will consider other factors that further affect the sensitivity and reliability of the test, such as contact area, skin site permeability, and occlusion, etc.

Dr. Don Bjerke, Chair of the CIR Science and Support Committee, delivered a wonderfully informative presentation titled "Skin Sensitization Risk Assessment and Confidence in New Approach Methodologies." The presentation provided interpretation of HRIPT data, emphasizing the importance of using dose per skin unit area as an appropriate dose metric for skin sensitization risk assessment, and further showcased the evolution and utilization of new approach methodologies (NAMs) for accessing skin sensitization risks. The presentation is available on the meeting page,

https://www.cir-safety.org/sites/default/files/166th%20CIR%20NAM%20Update%20Don%20Bjerke.pdf.

HAIR DYE EPIDEMIOLOGY

The Panel reviewed the revised draft of the Hair Dye Epidemiology Resource Document. The Panel restated its commitment to continuous surveillance of the latest epidemiological data concerning the association between personal hair dye use and human cancer risk. The Panel discussed the significance of the Hair Dye Epidemiology Resource Document as a living document for incorporating the forthcoming epidemiological data. The Panel determined the conclusion of the document would be periodically reassessed, in light of new information. Additionally, the Panel deliberated on broadening the document's influence by making it more accessible to the public. This document will be brought before the Panel again prior to finalization.

FDA and SCCS GUIDANCE

The Panel looked at 2 guidance documents, the *Draft Guidance for FDA Registration and Listing of Cosmetic Product Facilities and Products* (FDA Registration; FDA-2023-D-1716) and the *SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation - 12th revision* (SCCS NoG; SCCS/1647/22). The US FDA published their FDA Registration document to, in part, provide an opportunity for input on the creation of a new, mandatory cosmetic ingredient registration program. The Panel lauded this endeavor and looks forward to utilizing the resulting frequency of use data generated therein.

The Panel also thoroughly evaluated the SCCS NoG document and provided CIR Staff with significant input on the creation of a similar "CIR Notes of Guidance." This venture will assist CIR in their efforts to modernize.