ADMIN

Memo
Agenda
Minutes
Priorities

EXPERT PANEL MEETING
March 28-29, 2024

Commitment & Credibility since 1976

MEMORANDUM

To: The Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 168th Meeting of the Expert Panel — Thursday and Friday, March 28th – 29th, 2024
Date: March 4th, 2024

Welcome to the first Panel Meeting of 2024! The agenda and accompanying materials for the 168th Expert Panel Meeting, to be held on March 28th – 29th, 2024, are now available. ***The location is the same as our meeting in December*** – virtual, via the Microsoft Teams platform. **Again, *the meeting will start a little later than in the past; 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/168th-expert-panel-meeting

The meeting agenda includes the consideration of 8 reports advancing in the review process, including 1 final amended report, 1 tentative report, and 6 draft reports – 5 of which are re-opened reviews. Also, on the agenda are 3 rereview documents (1 report proposed for rereview and 2 rereview summaries). ***For the proposed rereview, 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.*** Furthermore, there are 5 additional administrative documents, including a Strategy Memo for the Dibutyl Phthalate review and one regarding Exposure Estimates; CIR Science and Support Committee (SSC) comments on risk assessments; the Draft 2025 Priorities; and a report from the Read-Across Working-Group.

Please note that the Read-Across Working Group, which comprises members of both Teams, is scheduled to meet from 1 – 2 PM (EST) on the first day of the meeting. Accordingly, team meetings will resume at 2:00.

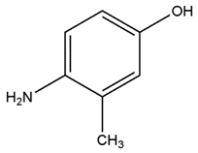
As stated in December, FDA's *Cosmetics Direct* mandatory reporting database deadline was extended, and now has a submission deadline of July 1, 2024. Accordingly, CIR will continue to utilize the FOU data received in 2023 from the VCRP until *Cosmetics Direct* is fully populated.

As we continue with our efforts to reduce the quantity of late breaking information, we are making a cutoff for nearly all information sent to the Panel. The exception to this cutoff is any pertinent information relevant to a Draft Final Report. (For this meeting, the only report that falls into that category is the Draft Final Amended Report on MIBK.) ***Submissions received on non-final reports, after the issuance of the Wave 2 supplement on March 18th, will be held back until the next Panel review of those reports.***

Finally, we would like to introduce you to the newest member of CIR. Dr. Thushara Diyabalanage joined CIR in January as a Senior Scientific Analyst to fill the vacancy created by Regina Tucker's departure last year. Thushara has a Ph.D. in Organic Chemistry from the University of South Florida, completed his postdoctoral fellowships at the Michigan State University (2007) and the NIH (2008-2012), and has previously worked at Actives International (a botanicals raw materials supplier). He has a great deal of scientific and writing experience, and looks forward to working with the Panel.

Draft Report - There are 6 draft reports for review. Sufficient data to proceed, or issue an Insufficient Data Announcement (IDA)?

1. 4-Amino-*m*-Cresol – DAR (Christina) – ***Dr. Belsito reports on day 2*** – The Panel first published a final report on 4-Amino-*m*-Cresol (along with 5 other cresol hair dyes) in 2004. In the original report, the Panel concluded that that the available data support the safety of 4-Amino-*m*-Cresol for use in oxidative and nonoxidative (semi-permanent) hair dyes. In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and at its June 2022 meeting, the Panel determined to reassess the safety of this ingredient.

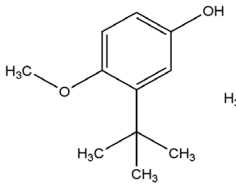


   According to 2023 VCRP survey data, 4-Amino-*m*-Cresol has 28 reported uses in hair dyes and colors. The results of the concentration of use survey conducted by the Council in 2021 reported that the maximum concentration of use range for 4-Amino-*m*-Cresol is 0.08 - 0.14% in hair dyes and colors. When the original safety assessment was published in 2004, 4-Amino-*m*-Cresol was reported to have no uses, according to 1998 VCRP data. However, according to industry data from 1999, 4-Amino-*m*-Cresol was reported to be used at up to 0.3% in hair dyes and colors.

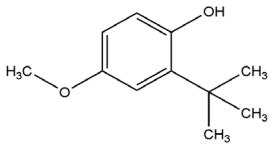
   Data from the original 2005 report on 4-Amino-*m*-Cresol have been summarized in this report, as appropriate, in *italicized* text.

   Upon review, 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, or unsafe 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. BHA – DAR (Preethi) – ***Dr. Belsito reports on day 2*** – The Panel first published a final report on Butylated Hydroxyanisole (since renamed BHA) in 1984, with the conclusion that it is safe as a cosmetic ingredient in the present practices of use (as described in the safety assessment). This conclusion was re-affirmed in 2003, as published in a rereview summary in 2006. In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and at its June 2023, meeting the Panel decided to reopen this safety assessment to evaluate potential endocrine and reproductive effects of BHA at high doses and to provide an updated assessment of this ingredient.



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



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

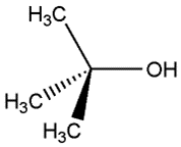
   BHA is mixture of tertiary butyl-substituted 4-methoxyphenols, consisting primarily of 3-*t*-butyl-4-hydroxyanisole (3-BHA) with lesser amounts of 2-*t*-butyl-4-hydroxyanisole (2-BHA). Thus, data found on BHA in both isomeric forms have been included (and identified), when available; in cases where the isomeric form is not known, the test article is simply described as BHA.

   This ingredient is reported to function in cosmetics as an antioxidant and a fragrance ingredient. Since the last review, reported use categories have not changed significantly and concentrations of use have remained constant over time, although the frequency of use has decreased considerably. According to 2023 VCRP data, BHA has 70 reported uses; at the time this ingredient was last considered for rereview, 1224 uses were reported. In 2023, the maximum reported concentration of use for BHA was 0.15% in other manicuring preparations; BHA was reported to be used at up to 0.2% in several product formulations (cologne and toilet waters, perfumes, blushers, and lipstick) in 2003. Jinqiu prepared a comparison of the daily exposure from BHA usage across 19 categories/types of cosmetic products to the acceptable daily intake (ADI) limit for BHA; this is included in the report for your consideration.

   Data from the original 1984 report and from the unpublished document evaluated by the Panel during their initial rereview deliberations have been summarized in this report, as appropriate, in *italicized* text.

   Upon review, 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 mixed 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. <u>*t*-Butyl Alcohol</u> – DAR (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel first published a final report on *t*-Butyl Alcohol in 1989; the available data were deemed insufficient to make a determination of safety. Subsequently, the Panel received additional data and published an amended final report in 2005, with the conclusion that on the basis of the available animal and clinical data in the report, *t*-Butyl Alcohol is safe as used in cosmetic products. In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and at its September 2023 meeting, the Panel decided to reopen this safety assessment to evaluate developmental and reproductive effects seen with exposure to 1% *t*-Butyl Alcohol, update the carcinogenicity discussion, and rectify an HRIPT concentration misstated in the Abstract. The Panel also noted an increase in reported uses and use concentrations, as well as a newly reported use in other baby products.

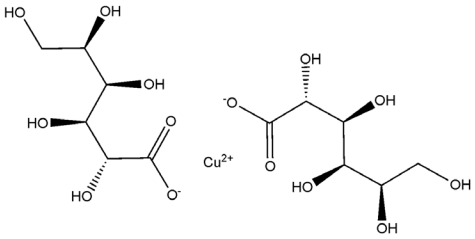


This ingredient is reported to function in cosmetics as a denaturant, fragrance ingredient, and solvent. The reported frequency and concentrations of use of t-Butyl Alcohol have increased since this ingredient was last considered. According to 2023 VCRP data, *t*-Butyl Alcohol has 136 reported uses, up from 32 reported uses in 1998. In 2023, the maximum reported concentration of use for *t*-Butyl Alcohol was 0.91% in aftershave lotions; in 1999, *t*-Butyl Alcohol was reported to be used at a maximum concentration of 0.5% in hair spray aerosol fixatives. An exposure assessment of *t*-Butyl Alcohol in 20 different cosmetic product use categories has been prepared by Jinqiu and is included in the report for the Panel's consideration.

Data from the original 2005 report on *t*-Butyl Alcohol have been summarized in this report, as appropriate, in *italicized* text.

Upon review, 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 mixed conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

4. <u>Copper Gluconate</u> – DR (Preethi) – ***Dr. Belsito reports on day 2*** – This is the first time the Panel has seen a safety assessment of this ingredient. A Scientific Literature Review (SLR) was announced by CIR on December 8, 2023.



This ingredient is reported to function in cosmetics as a skin-conditioning agent. According to 2023 VCRP survey data, Copper Gluconate has 170 reported uses, 140 of which are in leave-on formulations. The results of the concentration of use survey conducted by the Council in 2022 indicate that the maximum reported concentration of use for Copper Gluconate in a leave-on formulation is up at 0.006% in eyeliners; overall, the highest maximum reported concentration of use is 0.2% in baby shampoos. Jinqiu has performed an exposure assessment of daily copper exposure, resulting from the reported use of Copper Gluconate in cosmetics, to be utilized for comparison with the recommended daily allowance and tolerable upper limit values for copper oral intake.

Additionally, several quantitative structure-activity relationship (QSAR) models were described in European Chemicals Agency (ECHA) dossiers for repeated-dose and developmental and reproductive toxicity, and these have been included in this report. The Panel's thoughts on strategies for utilizing these predictive data are being sought.

Upon review, 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 mixed 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. <u>Lanolin-derived ingredients</u> – DAR (Christina) – ***Dr. Cohen reports on day 2*** – The Panel first published a final report on 9 lanolin-derived ingredients in 1980 with the conclusion 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). This conclusion was re-affirmed in 2003, as published in a rereview summary in 2005. In accordance with its Procedures, the Panel evaluates the conclusions of

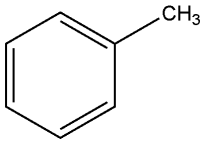
previously-issued reports approximately every 15 years, and at its June 2023 meeting, the Panel re-opened the safety assessment. Lanolin was named the Contact Allergen of the Year in 2023 by the American Contact Dermatitis Society

Most of the Lanolin-derived ingredients are reported to function in cosmetics as skin conditioning agents and hair conditioning agents; other cosmetic functions are also reported. According to 2023 VCRP survey data, Lanolin has the most reported uses in cosmetic products, with a total of 285 formulations, and Acetylated Lanolin Alcohol has the second most reported uses, with a total of 196; the majority of uses are in leave-on formulations. The frequencies of use for both of these ingredients have greatly changed since the Panel last considered these ingredients; at that time, Lanolin was reported to have 782 uses and Acetylated Lanolin Alcohol was reported to have 356 uses. The results of the concentration of use survey conducted by the Council in 2022 indicate Lanolin Oil has the highest maximum concentration of use in leave-on formulations; it is used at up to 47% in lipsticks. Lanolin is reported to be used at up to 40% in leave-on nail creams and lotions. When the Panel last considered these ingredients in 2003, the maximum leave-on use concentration for Lanolin Oil was 65% in lipstick; the maximum leave-on use concentration for Lanolin was 37% in body and hand skin care preparations.

Data from the original 1980 report and from the unpublished document evaluated by the Panel during their initial rereview deliberations have been summarized in this report, as appropriate, in *italicized* text.

Upon review, 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, mixed, 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.

6. Toluene – DAR (Priya) – ***Dr. Belsito reports on day 2*** – The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a final report on Toluene in 1987, with the conclusion that Toluene is safe in cosmetics in the present practices of use and concentration (as described in the safety assessment). This conclusion was re-affirmed in 2005, as published in a rereview summary in 2006. Following the March 2023 discussion of the draft 2024 Priorities List, CIR received communication from members of the FDA nominating Toluene to the 2024 Priority List, for cause. At its June 2023 meeting, the Panel agreed to accelerate a rereview on Toluene.



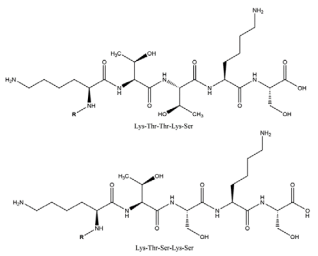
At its September 2023 meeting, the Panel reviewed a strategy memo and agreed to include studies published after 2005 in this amended report, while studies published between 1983 - 2005 were to be listed in a separate data appendix. That appendix is included with the report, and a document that includes the abstracts of each of these studies is being provided to the Panel via Google Drive (due to the size of the document and copyright limitations; please look for the link in your email from Kevin); for readers other than the Panel, these abstracts are all publicly available from the respective publishers. Additionally, data from the original 1987 report and data from the unpublished document evaluated by the Panel during their initial rereview deliberations have been summarized in this report, as appropriate, in *italicized* text.

This ingredient is reported to function in cosmetics as an antioxidant and a solvent. Since the initial rereview, the reported frequency and concentration of use have decreased. According to 2023 VCRP data, Toluene has 0 reported uses. However, according to the use survey conducted by the Council in 2022 - 2023, Toluene is reported to be used at up to 20% nail products, and in other products (e.g., bath, deodorant, baby products) at low concentrations. In comparison, 59 uses were reported to the VCRP in 2002, at a maximum concentration of 26%, with all uses reported to be in nail products. Jinqiu has provided risk assessment data exploring toxicity values and minimal risk levels of Toluene as well as a tiered approach for the calculation of a margin of safety (MoS) for use in nail products.

Upon review, 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 mixed 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 is 1 draft tentative report for consideration. Issue a tentative conclusion?

1. Pentapeptide ingredients – TR (Preethi) – ***Dr. Cohen reports on day 2*** – This is the second time the Panel has seen a safety assessment of these 3 cosmetic ingredients. As noted during the last review, data for 2 amino acid sequences of Pentapeptide-4 have been included, namely lysine-threonine-threonine-lysine-serine (KTTKS) and lysine-threonine-serine-lysine-serine (KTSKS), and the sequences used as the test article are indicated in the report. At the September 2023 meeting, the Panel issued an IDA with the following data needs:



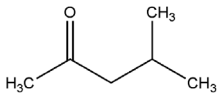
   - Dermal irritation and sensitization data for the KTSKS amino acid sequence
   - Skin penetration and degradation data for Myristoyl Pentapeptide-4 (KTSKS sequence)
   - Clarification of the concentration of use tested in the HRIPT study currently summarized in the report on Palmitoyl Pentapeptide-4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

   Since the last review, the corrected maximum reported concentration of use for these ingredients has been identified as 0.0035% Palmitoyl Pentapeptide-4 in hair conditioners; the highest reported leave-on concentration of use is now indicated to be 0.012% Palmitoyl Pentapeptide-4 in face and neck preparations (as opposed to 0.05% Myristoyl Pentapeptide-4 in other eye makeup products, which was previously reported). Additional data received include log P values, and summary HRIPT data for the study indicated in the IDA.

   The Panel should carefully consider and discuss the data (or lack thereof), and the draft Abstract and draft Discussion presented in this report. A Tentative Report with a safe as used, safe with qualifications, insufficient, mixed, split, or unsafe conclusion should then be issued.

Draft Final Report - There is 1 Draft Final Report for consideration. - Review this draft, especially the rationale provided in the Discussion section, and issue a final report, as appropriate.

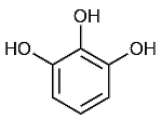
1. MIBK – FAR (Thushara) – ***Dr. Cohen reports on day 2*** – At the December 2023 meeting, the Panel issued a Tentative Amended Report reaffirming their original conclusion that MIBK is safe as used in nail care products and as an alcohol denaturant in cosmetics in the present practices of use and concentration described in this safety assessment. Because current concentrations of use are not reported, the expectation is that this ingredient would be used at concentrations comparable to that reported in the 2004 safety assessment. CIR has not received any new unpublished data.



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

Abbreviated Rereview (i.e., rereview proposal) – There is 1 rereview document. Because it has at least been 15 years since the previous review was published, in accordance with CIR Procedures, the Panel is only being asked if the report should be reopened.

1. Pyrogallol – RR (Christina) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of Pyrogallol in 1991 with the conclusion that Pyrogallol is safe as a cosmetic ingredient in the present practices of use and concentration. A rereview that was initiated in 2007 was tabled at the June 2007 Panel meeting to await the findings of the National Toxicology Program (NTP) 2-year carcinogenicity study. Unfortunately, although the NTP study was published in 2013, the rereview was never completed. However, accordingly, since it has now been at least 15 years since the initial rereview was presented to the Panel, the Panel is again asked to consider whether the safety assessment of Pyrogallol should be reopened.



   An extensive search of the world's literature was performed for studies dated 2004 forward. The Panel should consider the data found as a result of the search, as well as the results of the NTP study. A historical overview, comparison of the original and new use data, and a use table are enclosed herein.

At the time the original report was written, the maximum concentration of Pyrogallol allowed in hair dyes in Europe was 5.0%; however, European regulations regarding cosmetic ingredients now categorize Pyrogallol in Annex II, the list of substances prohibited in cosmetic products in Europe. Use of Pyrogallol since the initial rereview was performed has decreased. According to 2023 VCRP data, Pyrogallol was reported to be used in 1 "other" hair dye product. No concentrations of use were reported in the Council's 2022 survey.

If upon review of the new studies and updated use data the Panel determines that the Pyrogallol safety assessment should be re-opened for review, a draft amended report will be presented at an upcoming meeting.

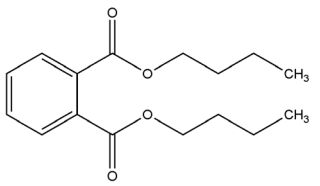
Administrative Items - there are 2 rereview summaries (presented together in 1 "RRsums" book) and 5 other administrative items.

RRsums - The Panel is being asked for editorial comment.

1. Sodium Carbonate – RRsum (Monice) – ***Dr. Belsito reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.
2. VA/Crotonates Copolymer – RRsum (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel should carefully consider the rereview summary and finalize it.

Other Admin

1. Dibutyl Phthalate – SM (Christina) – ***Dr. Belsito reports on day 2*** –



Following the March 2023 discussion of the draft 2024 Priorities List, CIR received communication from members of the FDA nominating Dibutyl Phthalate to the 2024 Priority List, for cause. At its June 2023 meeting, the Panel agreed to accelerate a rereview on Dibutyl Phthalate. The Panel first published a final report on Dibutyl Phthalate (and Dimethyl and Diethyl Phthalate) in 1985, and concluded that these ingredients are safe for topical application in the present practices of use and concentration in cosmetics. Upon rereview in 2002, the Panel reaffirmed the original conclusion, as published in 2005. In December 2012, the Panel deliberated on studies separately concerning endocrine disruption and diabetes and Dibutyl Phthalate, Diethyl Phthalate, Dimethyl Phthalate, and Butyl Benzyl Phthalate; however, the Panel chose not to re-open the safety assessment of these ingredients and published their discussion as a rereview summary in 2017.

   In preparation of the amended report, several questions have emerged that require Panel input. Specifically:

   - A substantial number of studies were discovered via a literature search of Dibutyl Phthalate dated 1999 forward, many including Diethyl Phthalate and/or Dimethyl Phthalate. Does the Panel want to include these two ingredients in this rereview?
     - If these ingredients are included, what additional data are needed for these ingredients?
   - Many of the studies focus on the potential effects of Dibutyl Phthalate on the endocrine system and reproductive and developmental effects. CIR is requesting Panel direction on the organization of these studies, as well as the study methodologies that should be included.

2. SSC risk comments – Admin (Jinqiu) – ***Dr. Cohen reports on day 2*** – The CIR SSC of the Personal Care Products Council (PCPC) submitted comments on Quantitative Systemic Risk Assessments and Models Used in Draft Systemic Quantitative Risk Assessments. The Panel is being asked to consider the CIR SSC's comments in the submission, and to take into account their recommendations for carrying out exposure and quantitative risk assessments as part of the report evaluation process.

3. Exposure – SM (Jinqiu) – ***Dr. Belsito reports on day 2*** – As pointed out by the SSC and in PCPC comments, although CIR reports feature a table that outlines the frequency and concentration of use of the ingredient across different product categories based on FDA's database, this information by itself does not directly reveal the levels of exposure. It was suggested that the products for

which risk assessments are completed should be those resulting in the highest exposure, rather than the products with the highest concentration; specifically, under in-use exposure scenarios, assessing exposure involves more than just the concentration of use.

The Panel is being asked to consider the utility of including a table in CIR reports that features exposure estimates across various product categories, particularly focusing on external exposure for dermal uptake. Examples of such tables are included in several reports being presented at this meeting (e.g., the BHA and *t*-Butyl Alcohol reports). If deemed useful, the Panel is requested to also decide on the preferred product type to use in cases where specific information on cosmetics exposure is lacking.

4. Priorities (Draft) – Admin (Bart) – ***Dr. Cohen reports on day 2*** – A draft Priority List is routinely presented to the Panel at the first meeting of the year, in accordance with CIR Procedures. However, currently, there are 18 reports docketed, covering 31 ingredients, remaining on the 2024 Final Priorities List. Additionally, there are reports that were previously-prioritized still remaining on the CIR docket, an extensive number of rereviews to be evaluated, as well as new methodologies and technologies to be explored. Accordingly, CIR is proposing that the existing workload will carry through 2025, and that no reports be added to the 2025 Priority List based on frequency-of-use; prioritization of ingredients nominated for cause will still be considered. Additionally, this strategy will allow for the next Priority List to utilize the mandatory reporting data that will be submitted to *Cosmetics Direct*, as opposed to the outdated information that would be obtained from the now defunct VCRP.

5. Read-Across – Admin (Bart) – ***Working Group reports on day 2*** – The Read-Across Working-Group (RAWG) is being convened for the first time at this meeting. This sub-group of the Panel is being asked to discuss general parameters that they would require in submissions where a read-across strategy is proposed. Additionally, input is being sought as to how the use of read-across strategies be should presented in CIR reports.

Full Panel Meeting

The Panel will consider the 1 report to potentially be issued as a Final Report, followed by the remaining reports advancing in the process (i.e., the Tentative Report and Draft Reports). In addition, a consensus should be reached for the 1 rereview document, the 2 rereview summaries, and the 5 other administrative items.

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

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

Agenda
168th Meeting of the Expert Panel for Cosmetic Ingredient Safety
March 28th – 29th, 2024

Thursday, March 28, 2024		
9:30 AM	**WELCOME TO THE 168th EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
9:45 AM - 12 PM	**TEAM MEETINGS**	**Drs. Belsito/Cohen**
12 PM – 1 PM	**Lunch break**	
1 PM – 2 PM	**READ-ACROSS WORKING-GROUP MEETING***	**Drs. Klaassen/Rettie/Ross/Tilton**
2 PM - 6 PM	**TEAM MEETINGS (continued)**	**Drs. Belsito/Cohen**

Dr. Belsito's Team**

DAR (CB)	Lanolin
DAR (CB)	4-Amino-*m*-Cresol
RR (CB)	Pyrogallol
SM (CB)	Dibutyl Phthalate
DAR (PC)	Toluene
RRsum (MF|BH)	Sodium Carbonate
Admin (MF|BH)	Draft 2025 Priorities
Admin (JZ)	SSC risk comments
SM (JZ)	Exposure
DR (PR)	Copper Gluconate
DAR (PR)	*t*-Butyl Alcohol
DAR (PR)	BHA
TR (PR)	Pentapeptides
RRsum (PR|MF|BH)	VA/Crotonates Copolymer
FAR (TD)	MIBK

Dr. Cohen's Team

Admin (JZ)	SSC risk comments
SM (JZ)	Exposure
DR (PR)	Copper Gluconate
DAR (PR)	*t*-Butyl Alcohol
DAR (PR)	BHA
TR (PR)	Pentapeptides
RRsum (PR|BH|MF)	VA/Crotonates Copolymer
Admin (BH|MF)	Draft 2025 Priorities
RRsum (BH|MF)	Sodium Carbonate
FAR (TD)	MIBK
DAR (PC)	Toluene
DAR (CB)	Lanolin
DAR (CB)	4-Amino-*m*-Cresol
RR (CB)	Pyrogallol
SM (CB)	Dibutyl Phthalate

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

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

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

*The Read-Across Working-Group will convene in Cohen Team Breakout virtual room from 1 to 2 PM, to discuss general read-across matters.
**Team moves to the breakout room. For the virtual meeting, that is a separate Teams meeting room.

Friday, March 29, 2024			
9:30 AM	**WELCOME TO THE 168th FULL EXPERT PANEL MEETING**		**Dr. Bergfeld**
9:40 AM	Admin **MINUTES OF THE DECEMBER 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 (TD)	MIBK – ***Dr. Cohen reports***	
	Reports Advancing		
	DAR (PC)	Toluene – ***Dr. Belsito reports***	
	TR (PR)	Pentapeptide ingredients – ***Dr. Cohen reports***	
	DR (PR)	Copper Gluconate – ***Dr. Belsito reports***	
	DAR (PR)	*t*-Butyl Alcohol – ***Dr. Cohen reports***	
	DAR (PR)	BHA ***– Dr. Belsito reports***	
	DAR (CB)	Lanolin ***- Dr. Cohen reports***	
	DAR (CB)	4-Amino-*m*-Cresol – ***Dr. Belsito reports***	
	Other Items		
	RR (CB)	Pyrogallol – ***Dr. Cohen reports***	
	RRsum (MF)	Sodium Carbonate – ***Dr. Belsito reports***	
	RRsum (PR)	VA/Crotonates Copolymer – ***Dr. Cohen reports***	
	SM (CB)	Dibutyl Phthalate ***- Dr. Belsito reports***	
	Admin (JZ)	SSC risk comments – ***Dr. Cohen reports***	
	SM (JZ)	Exposure – ***Dr. Belsito reports***	
	Admin (BH)	Priorities (Draft) – ***Dr. Cohen reports***	
	Admin (BH)	Read-Across – ***Working-Group reports***	

ADJOURN – *The next will be held in-person on **June 3 – 4, 2024** at the Westin Georgetown Hotel, 2350 M Street, N.W., 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 || TD: Thushara Diyabalanage || PR: Preethi Raj || JZ: Jinqiu Zhu

ONE HUNDRED SIXTY-SEVENTH MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

December 4-5, 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

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*
David Abramovitz	Locke Lord
Jennifer Ator	Combe
John Bailey	JEB Consulting
Don Bjerke	Procter & Gamble
AJ Cuevas	Combe
Silvia Pérez Damonte	CLAIM
Thushara Diyabalanage	CIR
Sara Eglitis	Enhanced Compliance, Inc.
Carol Eisenmann	Personal Care Products Council
Christine Maza Ferrerira	unidentified
Linda Giles	Transcription, Etc.
Richard Grabarz	Combe
Ji Hye Han	unidentified
Karen Iveson	Combe
Jung Eun Ji	unidentified
Sarah Kickham	Combe
HJ Kim	unidentified
Kyoungok Kim	Korea Cosmetic Association
Giorgia La Rosa	Angel Consulting SAS
Miao Li	unidentified
Jessica Madrigal	unidentified
Ines Messina	Angel Consulting SAS
Kris Miles	Nouryon
Sanghamitra Mishra	unidentified
Jeffrey Nicolai	Performance Beauty Group
Thomas Petry	ToxMinds BVBA
Audrey Pokrzywa	Silab
Carol Pratt	unidentified
Padmaja Prem	Combe
Pushpa Rao	Combe
Federica Robino	Angel Consulting SAS
Mona Rose	unidentified
Alexandra Gorman Scranton	Women's Voices for the Earth
Anthony Santini	Combe
Prajakta Shimpi	L'Oreal USA
Brenda Shinyashiki	Edgewell Personal Care
Caterina Soffiotto	Angel Consulting SAS
Marina Souza	unidentified
Kathy Stanton	Personal Care Products Council
Christine Thiffault	Exponent
Liz Toledo	unidentified
Laura Turnham	Swift Fox Consultancy
Chiara Vinci	Thermo Fisher Scientific
Zemin Wang	US FDA
Joseph Wang	unidentified
Teresa Washington	unidentified
Craig Weiss	CPTC
Hong Xie	US FDA
Merle Zimmermann	American Herbal Products Association

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 167th meeting of the Expert Panel for Cosmetic Ingredient Safety and wished everyone a happy holiday season. Dr. Bergfeld noted that the Panel hosted 5 guest speakers at this meeting and reviewed 14 documents, including 8 ingredient reports and 6 re-review packages or re-review summaries. Several of the ingredient reports had risk assessment (margin of safety) discussions that the Panel utilized to evaluate the safety of the ingredients therein. Dr. Bergfeld also noted that the Yeast safety assessment used a QPS, or presumed safe, methodology to aid in determining which of the many ingredients in the report were safe for use in cosmetic products. The Panel also reviewed 3 resource documents, including those of inhalation exposure, nitrosation, and analytical tools. Dr. Bergfeld thanked former Panel member, Dr. Ron Shank, for his help in editing the nitrosation resource document.

Dr. Bergfeld thanked the CIR staff, the CIR Science and Support Committee, the Council, and the Panel for their efforts in preparation for this meeting. Dr. Bergfeld expressed appreciation on behalf of the Panel that no late submissions of data (Wave 3) were received.

APPROVAL OF MINUTES

The minutes of the September 11-12, 2023 (166th) Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth thanked the members of and liaisons to the Expert Panel for Cosmetic Ingredient Safety. He noted that for this meeting, CIR had taken a couple of steps to make the workload more manageable, including reducing the number of reports in progress and placing a firm cut-off for late submissions. He also confirmed that these steps would continue to be utilized.

CIR and the Panel have previously discussed the value and relevance of the MoCRA legislation of 2022, and how quickly the deadline to submit ingredient registrations was looming. Fortunately, this deadline has been pushed back until July 2024. Additionally, along with the updated regulatory authority provided by MoCRA, FDA is proposing a ban on the use of formaldehyde in hair-straightening formulations, in full agreement with this Panel's conclusion in the Formaldehyde and Methylene Glycol report. This is particularly important as these products are targeted at certain communities, and it is paramount that these consumers are protected. CIR applauds this progress.

As a member of the CIR Steering Committee, the president of the Personal Care Products Council (PCPC) plays an important role as a member therein. Dr. Heldreth stated that CIR and the Panel have been fortunate to have Lezlee Westine in that role over the last decade, who played a major role in the MoCRA legislation. Lezlee will be retiring at the end of this year and Tom Myers, currently PCPC's Executive Vice President for Legal & Regulatory Affairs and General Counsel, will be the Council's new president starting in 2024. Dr. Heldreth stated that he has been fortunate to consult with Tom over the years, and wanted to express how very fortunate CIR and the Panel are to have him stepping into these new roles.

On the agenda at this meeting were 5 speakers covering 1,2,4-Trihydroxybenzene and Prostaglandins. First up was Dr. AJ Cuevas, Combe Sr. Manager Global Product Safety, who delivered a presentation titled "1,2,4-THB – Comprehensive Review of Chemical & Toxicological Data CIR Expert Panel Meeting." Following a Q&A session thereon, Mr. Craig Weiss, President CPTC, and Mr. David Abramovitz, Partner Locke Lord, presented "New Studies Support Safety of Isopropyl Cloprostenate in Cosmetics." Finally, Dr. Thomas Petry, Managing Director ToxMinds BVBA and Ms. Sanghamitra Mishra, ERT, Senior Consultant at ToxMinds presented "Safety Assessment of Ethyl Tafluprostamide as Used in Cosmetic Products." Following these presentations, there were 8 reports advancing in the review process with a great deal of input from the speakers. There were also a number of administrative items, including resources documents on Nitrosation and Inhalation, and a Strategy Memo regarding various in silico tools. The CIR Staff have already started investigating some of the new in silico tools, with plans to investigate more to better support this Panel.

FINAL SAFETY ASSESSMENTS

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

The Panel issued a Final Amended Report with the conclusion that 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl are safe for use as hair dye ingredients in the present practices of use and concentration described in the safety assessment. The Panel previously reviewed 5-Amino-4-Chloro-*o*-Cresol 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 are now presented as individual stand-alone reports. Much of the data on 5-Amino-4-Chloro-o-Cresol in the original report was actually on the salt, 5-Amino-4-Chloro-*o*-Cresol HCl. Accordingly, 5-Amino-4-Chloro-*o*-Cresol HCl is included in this amended report because in situ and in formulation, the salt and free base are identical.

5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl are reported to function as oxidative hair dyes in hair coloring products. While no uses are currently reported, previous use data indicated 5-Amino-4-Chloro-*o*-Cresol was used at 1% in hair dyes and colors. The Panel recognizes that hair dyes containing these ingredients, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the US 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.

While results of in vivo micronucleus studies were negative, in vitro genotoxicity studies yielded mixed results; however, concern for these mixed results was mitigated by the weight-of-evidence (WoE) of negative results for other toxicity endpoints. The Panel noted the lack of method of manufacturing information, but data on composition and impurities for these ingredients and the high degree of reported purity mitigated this need. The Panel performed a conservative margin of safety (MOS) calculation using the assumption of 50% absorption of 5-Amino-4-Chloro-*o*-Cresol HCl and daily application. The resulting MOS for 5-Amino-4-Chloro-*o*-Cresol HCl formulated at 1% is 217, which is considered protective.

Plant-Derived Charcoal Ingredients

The Panel issued a Final Report with the conclusion that the following 3 plant-derived Charcoal ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Charcoal Charcoal Extract Charcoal Powder

These ingredients, as used in cosmetics, comprise carbonaceous materials produced by the pyrolysis of plant-derived organic matter. Only plant-derived charcoal ingredients are included in this assessment; accordingly, charcoal derived from petroleum or other mineral sources are excluded from this review.

The International Nomenclature Committee (INC) has determined that activated charcoal is a synonym for Charcoal Powder, and is listed as such in the *Dictionary*.

TENTATIVE SAFETY ASSESSMENTS

1,2,4-Trihydroxybenzene
The Panel issued a Tentative Report for public comment with the conclusion that 1,2,4-Trihydroxybenzene is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment. According to 2023 VCRP survey data, this ingredient 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.

1,2,4-Trihydroxybenzene is reported to function as an 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 while results of in vivo micronucleus studies were negative, in vitro genotoxicity studies yielded mixed results; however, concern for these mixed results was mitigated by the WoE of negative results for other toxicity endpoints. The Panel performed a conservative MOS calculation using lowest-observed-adverse-effect-level (LOAEL) of 50 mg/kg bw/d as a Point of Departure (PoD), an assessment factor of 3 for extrapolation from LOAEL to no-observed-adverse-effect-level (NOAEL), and the dermal absorption per treatment of 2.5% Trihydroxybenzene of 2.15 mg. The resulting MOS is 466, well above the accepted risk threshold of 100, and is considered protective.

Yeast-Derived Ingredients
The Panel issued a Tentative Report for public comment with a split conclusion of safety for these 56 yeast-derived ingredients. Ingredients in which both dermal sensitization data and food use/generally recognized as safe (GRAS)/qualified presumption of safety (QPS) status were considered safe in the present practices of use and concentration described in the assessment. These ingredients include the following:

Hydrolyzed Candida Saitoana Extract
Galactomyces Ferment Filtrate
Hydrolyzed Metschnikowia Agaves Extract
Metschnikowia Agaves Extract
Hydrolyzed Metschnikowia Reukaufii Extract
Metschnikowia Reukaufii Lysate Extract
Phaffia Rhodozyma Extract
Phaffia Rhodozyma Ferment Extract
Pichia Anomala Extract
Pichia Minuta Extract
Saccharomyces Cerevisiae Extract

Also considered safe were the following 22 generic-named yeast-derived ingredients (ingredients in which the species of yeast used in manufacturing was not provided in the *Dictionary*), when derived from species of yeast included in the report, with both dermal sensitization and food use/GRAS/QPS status.

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

It should be noted that data remain insufficient to conclude on the safety of the generic ingredients listed above when the species used to manufacture these ingredients do not have dermal sensitization data and food use/GRAS/QPS status. Data were also considered insufficient for the following 23 ingredients:

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

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

***p*-Phenylenediamine, *p*-Phenylenediamine HCl, and *p*-Phenylenediamine Sulfate**
The Panel issued a Tentative Amended Report for public comment with the conclusion that the following ingredients are safe for use as hair dye ingredients in the present practices of use and concentration described in the safety assessment:

p-Phenylenediamine *p*-Phenylenediamine HCl *p*-Phenylenediamine Sulfate

According to 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, 7 uses have been reported for eye makeup preparations. Only 1 use was reported in a hair coloring shampoo for the HCl salt and no uses were reported for the sulfate salt. 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 related salts.

With regard to the reported use in eye makeup preparations, the FD&C Act mandates that color additives must be approved by FDA for their intended use before they are used. The Panel has also noted that *p*-Phenylenediamine has been used as a dye in black henna temporary tattoos. *p*-Phenylenediamine is an unapproved color additive in cosmetics products (including in eye makeup preparations and tattoos), and thereby, such uses are not permitted according to the Act. These uses are not within the purview of this Panel.

These ingredients are reported to function as oxidative hair dyes in hair coloring products. The Panel recognizes that hair dyes containing these ingredients, 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.

MIBK
The Panel issued a Tentative Amended Report for public comment with the conclusion that MIBK is safe as used in nail care products and as an alcohol denaturant in cosmetics in the present practices of use and concentration described in the safety assessment.

At the June 2023 meeting, an Insufficient Data Announcement (IDA) on MIBK was issued. Concentration of use and function, in aftershave formulations, and confirmatory sensitization studies at the maximum use concentration, were requested. No new data was received or found. The Panel noted that use in the aftershave product is safe if the function is as an alcohol denaturant. Additionally, the Panel reiterated that when used as an alcohol denaturant, MIBK should not be used at more than 4%.

INSUFFICIENT DATA ANNOUNCEMENTS

Prostaglandin Analogues
The Panel issued a second IDA for Isopropyl Cloprostenate and Ethyl Tafluprostamide. In order to determine the safety of Isopropyl Cloprostenate, the Panel requires the following data:

- dermal irritation and sensitization data at the current maximum concentration use of 0.0075%
- data on local ocular effects (intraocular pressure, iris color change, and periorbital fat loss) at current maximum concentration of use o
    - independent ophthalmologist to assess colorimetric data regarding iris color change
- acute toxicity data
- repeated dose toxicity data
- developmental and reproductive toxicity data
- in vitro and in vivo genotoxicity data

In order to determine the safety of Ethyl Tafluprostamide, the Panel requires:

- acute toxicity data
- repeated dose toxicity data
- developmental and reproductive toxicity data
- in vivo genotoxicity data

Fulfillment of the above data needs is preferred; however, the Panel noted suggestions from industry regarding the use of read-across source to fill in toxicological data gaps for these prostaglandin ingredients. The Panel acknowledged they would consider confirmatory data (e.g., receptor interaction studies and downstream profiles of adverse effects) to determine if the use of the proposed read-across sources is appropriate to target the ingredients in this report. Lastly, robust information on possible targets and mechanisms regarding these ingredients are requested for both Isopropyl Cloprostenate and Ethyl Tafluprostamide.

TABLED REPORT

Octoxynols
The Panel determined that the Draft Amended Report of the following 25 octoxynol ingredients should be tabled until updated use data are available via reporting in the Cosmetics Direct database, as mandated in a forthcoming initiative of the Modernization of Cosmetic Regulation Act of 2022 (MoCRA).

Octoxynol-3	Octoxynol-10	Octoxynol-25
Octoxynol-5	Octoxynol-11	Octoxynol-30
Octoxynol-6	Octoxynol-12	Octoxynol-33
Octoxynol-7	Octoxynol-13	Octoxynol-40
Octoxynol-8	Octoxynol-16	Octoxynol-70
Octoxynol-9	Octoxynol-20	Octoxynol-9 Carboxylic Acid

Octoxynol-20 Carboxylic Acid
Potassium Octoxynol-12 Phosphate
Sodium Octoxynol-2 Ethane Sulfonate
Sodium Octoxynol-2 Sulfate
Sodium Octoxynol-6 Sulfate
Sodium Octoxynol-9 Sulfate

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 2 previous assessments for re-review. In both cases, the Panel reaffirmed the conclusions reached for these 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.

- Sodium Carbonate – 3 ingredients
- VA/Crotonates Copolymer – 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 4 re-review summaries:

- Zinc Phenolsulfonate
- Isobutane
- Laneth-10 Acetate
- Sodium Dehydroacetate

INHALATION RESOURCE DOCUMENT

The Panel reviewed the revised Inhalation Resource Document and discussed the newly incorporated particle size data of certain propellant-driven sprays. The Panel noted spray products associated with innovative formulations and advanced nozzle techniques may release aerosols with increasing proportion of respirable particles (e.g., dry shampoo and airbrush devices). The Panel recognized the importance of characterizing the relevant spray devices and better understanding the advancement of analytical methods to accurately examine the particle size distribution under realistic use conditions. The Panel will closely monitor the new particle size distribution data of these products, along with the development of analytical techniques for measuring the fine and ultrafine particles emitted by sprayable cosmetic products. The Panel contemplated requesting more information and clarification about device application and exposure parameters from industry and the FDA Office of Devices. Following the acquisition of further information and input, the Panel plans to revise the respiratory boilerplate language to reflect their comprehension of the risks associated with incidental inhalation. Furthermore, the Panel will implement further editorial revisions for enhancing the document's conciseness and readability.

NITROSATION RESOURCE DOCUMENT

The Panel reviewed a revised Nitrosation Resource Document and agreed to open it for a 60-day period of public comment. The Panel expressed their appreciation to Dr. Ron Shank for his invaluable contribution in revising the document. The Panel further discussed the necessity of clarifying certain strategies for minimizing nitrosation, which are recommended for formulators, as well as the necessity of clarifying the presence of certain nitrosatable precursors which may exist as impurities in raw materials. Upon considering and addressing any feedback received during the public comment period, this document will be presented to the Panel again for further review.

TOOLS STRATEGY

The Panel discussed the possible application of certain in silico tools identified by the CIR Science and Support Committee (SSC) for searching data and assessing the risk and safety of cosmetic ingredients. The Panel further discussed the limitations of in silico assessments in terms of reliability and relevance for data gap filling. The Panel agreed results obtained from certain in silico tools would be considered as additional resources in a WoE approach to derive robust conclusions.

Commitment & Credibility since 1976

Memorandum

Date: March 4th, 2024

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

To: All Stakeholders

Re: 2025 Draft Priority List

There are 18 reports docketed, covering 31 ingredients, on the 2024 Final Priorities List. While the priority list includes only the lead ingredients, groupings of ingredients for reports can be found on the following pages. Reports previously prioritized and on the CIR docket, 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, and beyond. Additionally, with modernization efforts to better utilize in silico tools (e.g., DEREK), NAMs (new approach/non-animal methodologies), *Cosmetics Direct* (the US FDA mandatory reporting program to replace the now defunct voluntary program, VCRP), formalized exposure and risk assessments (when warranted), and read-across (including proposals of the Read-Across Working-Group), we believe that there is plenty of substance on the Panel's docket to extend through the end of 2025.

Accordingly, we propose no frequency-of-use-based ingredient report additions to the Panel's docket in the coming year. However, if any interested party would like to request an ingredient review for cause (including: highlighting a potential risk/safety concern, accompanied with supporting data/information), we would be happy to present these to the Panel for potential prioritization. To make a request for cause, please provide a complete submission to CIR no later than May 3rd, 2024.

Thus, interested parties are yet encouraged to submit pertinent data to the CIR, as soon as possible, for use in the development of the Scientific Literature Reviews (SLR), and to participate in meetings of the Panel, for the ingredients on the 2024 Final Priorities List. 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
- Exposure and risk
- Toxicokinetics data, specifically dermal absorption and 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 natural complex substances (NCS), including botanical ingredients, the additional data needed include: species, organism 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**

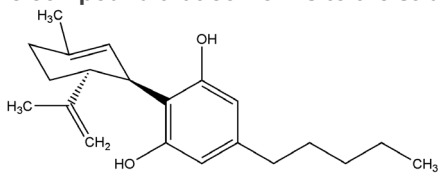
2024/2025 Final Priorities Groupings for New Reports

Planned 2024/2025 Reports – per cause

Cannabidiol – *Previously proposed for Panel review by FDA*

→Cannabidiol (CBD) **FOU = 32**

Definition: Cannabidiol is the organic compound that conforms to the structure:



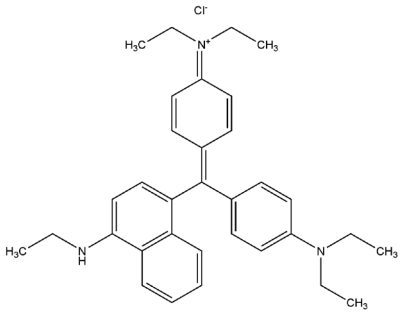
Reported **Functions**: Antiacne Agents; Antioxidants; Drug Astringents - Skin Protectant Drugs; Skin Protectants; Skin-Conditioning Agents - Miscellaneous

Notes: *(CAS No. 13956-29-1) At a previous meeting, a liaison from the FDA proposed that the Panel assess the safety of Cannabidiol (CBD). At that time, there were zero formulations reported to the VCRP containing cannabinoid ingredients; accordingly, the Panel chose to defer review.*

Grouping proposal: None

Basic Blue 7 – on EU Annex II – forbidden from use in cosmetics **FOU = 1**

Definition: Basic Blue 7 is classed chemically as a triarylmethane color. It conforms to the structure:



Reported **Function**: Hair Colorant

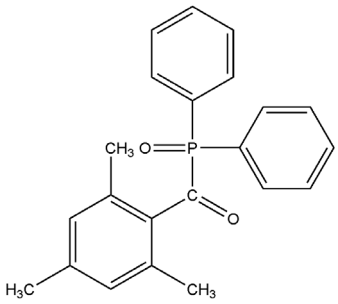
Notes: *(CAS No. 2390-60-5) on EU Annex II – forbidden from use in cosmetics*

Grouping proposal: None

Trimethylbenzoyl Diphenylphosphine Oxide – *FDA request*

FOU = 127

Definition: Trimethylbenzoyl Diphenylphosphine Oxide is the organic compound that conforms to the structure:



Reported **Function**: Skin Conditioning Agent

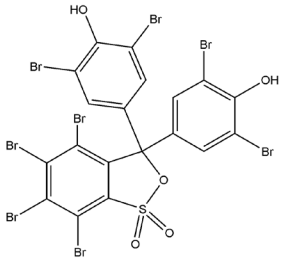
Notes: *ECHA launched a 45-d consultation for their plan for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (Trimethylbenzoyl Diphenylphosphine Oxide) to be added to the substances of very high concern (SVHC) list on February 17, 2023. There are new DART concerns.*

Grouping proposal: None

Tetrabromophenol Blue – SCCS insufficient data

FOU = 2

Definition: Tetrabromophenol Blue is the organic compound that conforms to the structure:



Reported **Function**: Hair Colorant

Notes: *(CAS No. 4430-25-5) There is a 2019 SCCS opinion (https://health.ec.europa.eu/system/files/2021-08/sccs_o_232_0.pdf) with a conclusion of safe when used as a hair dye in oxidative and non-oxidative hair coloring products at a final on-head concentration of up to 0.2%. Tetrabromophenol Blue has also been added to EU Annex III (entry 319) with the limitations recommended by the SCCS in 2019.*

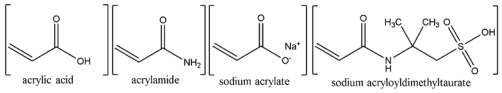
Grouping proposal: None

Planned 2024/2025 Reports – per FOU

Polyacrylate-13

FOU = 265

Definition: Polyacrylate-13 is the copolymer of acrylic acid, acrylamide, sodium acrylate, and sodium acryloyldimethyltaurate monomers.



Reported **Function**: Film Formers

Notes: *The Panel has previously assessed the safety of structurally similar ingredients in the Safety Assessment of Acryloyldimethyltaurate Polymers as Used in Cosmetics, finalized in 2017 (e.g., Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer, defined as: a copolymer of acrylamide, sodium acryloyldimethyltaurate, and acrylic acid monomers), concluding that such copolymers are safe as used.*

Grouping proposal: None

Polygonum Cuspidatum Root Extract

FOU = 245

Definition: Polygonum Cuspidatum Root Extract is the extract of the roots of *Polygonum cuspidatum.* The accepted scientific name for *Polygonum cuspidatum* is *Fallopia japonica.*

Reported **Functions**: Antioxidants; Skin-Conditioning Agents – Miscellaneous

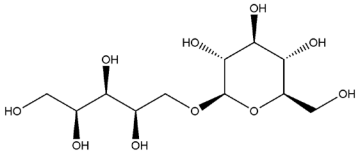
Notes: *These 2 botanical ingredients are derived from the same plant species, 1 from the root and the other from the whole plant.*

CIR draft grouping/clustering: (2 ingredients proposed with a total FOU = 245)	***FOU***
Polygonum Cuspidatum Root Extract	*245*
Polygonum Cuspidatum Extract	-

Xylitylglucoside

FOU = 213

Definition: Xylitylglucoside is the organic compound that conforms to the structure:



Reported **Functions**: Skin-Conditioning Agents - Humectant

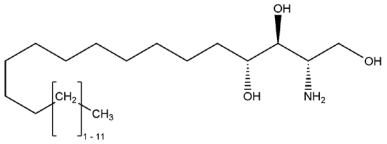
Notes: *(CAS No. 1095751-96-4)*

CIR draft grouping: None

Phytosphingosine

FOU = 210

Definition: Phytosphingosine is a synthetic sphingolipid that conforms generally to the structure:



***Reported* Functions**: Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous

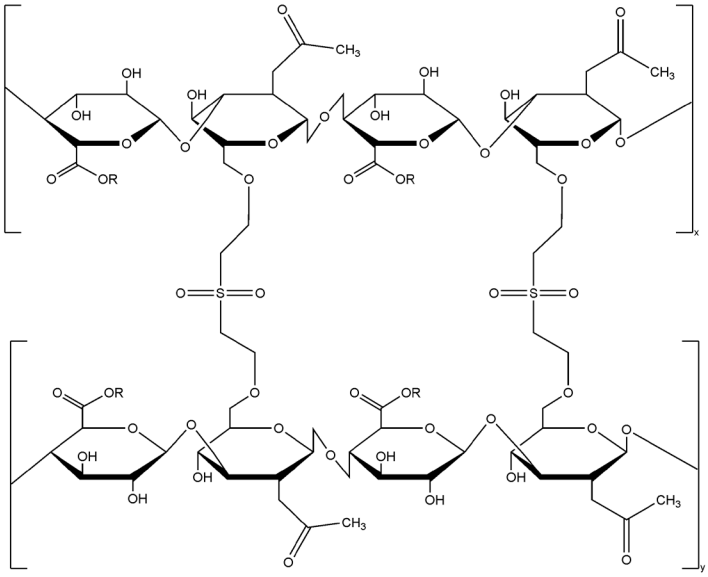
Notes: *(CAS Nos. 554-62-1; 13552-11-9) The Panel has previously assessed the safety of structurally-related ingredients in the Safety Assessment of Ceramides as Used in Cosmetics, published in IJT in 2020 (e.g., Caprooyl Phytosphingosine, defined as: the product obtained by the reaction of Caproic Acid and Phytosphingosine), concluding that such copolymers are safe as used. While Phytosphingosine contains a free amine functional group, the ceramides differ as corresponding amides.*

CIR draft grouping: (4 ingredients proposed with a total FOU = 233)	***FOU***
Phytosphingosine	*210*
Tetraacetylphytosphingosine	*17*
Acetylphytosphingosine	*4*
Phytosphingosine HCl	*2*

Sodium Hyaluronate Crosspolymer

FOU = 207

Definition: Sodium Hyaluronate Crosspolymer is the sodium salt of a polymer of Hyaluronic Acid crosslinked with *di*vinyl sulfone.



wherein R is hydrogen or sodium

***Reported* Functions**: Skin-Conditioning Agents – Humectant; Skin-Conditioning Agents - Miscellaneous

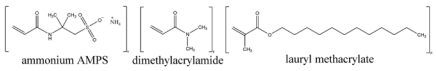
Notes: *(CAS No. 105524-32-1) These 3 ingredients share the same polyhyaluronate backbone and differ only by the crosslinker (diglycidyl ether for Sodium Hyaluronate Crosspolymer-2 and propylbisoxyamine for Sodium Hyaluronate Crosspolymer-3). (The Panel has recently addressed the safety of Sodium Hyaluronate.)*

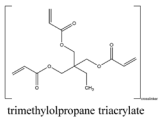
CIR draft grouping: (3 ingredients proposed with a total FOU = 210)	***FOU***
Sodium Hyaluronate Crosspolymer	*207*
Sodium Hyaluronate Crosspolymer-2	*2*
Sodium Hyaluronate Crosspolymer-3	*1*

Polyacrylate Crosspolymer-6

FOU = 205

Definition: Polyacrylate Crosspolymer-6 is a copolymer of ammonium AMPS (2-acrylamido-2-methylpropane sulfonic acid), dimethylacrylamide, lauryl methacrylate, and laureth-4 methacrylate, crosslinked with trimethylolpropane triacrylate.





Reported **Functions**: Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous

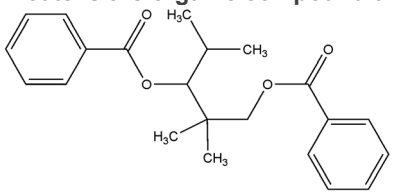
Notes:

CIR draft grouping: none

Trimethylpentanediyl Dibenzoate

FOU = 202

Definition: Trimethylpentanediyl Dibenzoate is the organic compound that conforms to the structure:



Reported **Functions**: Plasticizers

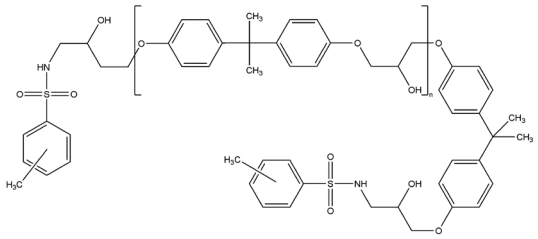
Notes: *(CAS No. 68052-23-3)*

CIR draft grouping: none

Tosylamide/Epoxy Resin

FOU = 189

Definition: Tosylamide/Epoxy Resin is the toluenesulfonamide of the condensation product of 4,4'-isopropylidenediphenol/epichlorohydrin copolymer, also known as the epoxy resin. The polymeric end-product conforms generally to the structure:



wherein n = 0 to 5

Reported **Functions**: Dispersing Agents – Nonsurfactant; Film Formers; Plasticizers

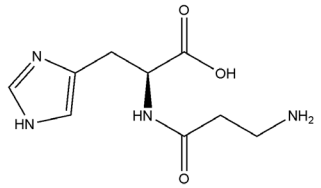
Notes: *According to chemical structure, minimum molecular weight is 1012 Da.*

CIR draft grouping: none

Carnosine

FOU = 184

Definition: Carnosine is the heterocyclic amine that conforms to the structure:



Reported **Functions**: Skin-Conditioning Agents - Miscellaneous

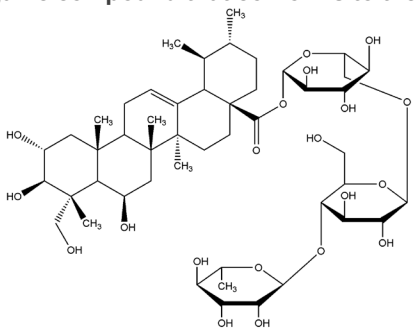
Notes: *(CAS No. 305-84-0)*

CIR draft grouping: None

Madecassoside

FOU = 182

Definition: Madecassoside is the organic compound that conforms to the structure:



Reported **Function**: Antioxidants; Skin Protectants; Skin-Conditioning Agents - Miscellaneous

Notes: (*CAS No. 34540-22-2*)

Grouping proposal: None

Sophora Flavescens Root Extract

FOU = 179

Definition: Sophora Flavescens Root Extract is the extract of the roots of *Sophora flavescens*.

Reported **Functions**: Antioxidants; Skin-Conditioning Agents – Miscellaneous

Notes: *These 3 botanical ingredients are each from the same species, Sophora flavescens, sometimes referred to as shrubby sophora. Of these 3, 2 ingredients are derived from the root, and the other is derived from the whole plant.*

CIR draft grouping: (3 ingredients proposed with a total FOU = 220)	***FOU***
Sophora Flavescens Root Extract	*179*
Sophora Flavescens Extract	*40*
Sophora Flavescens Root Powder	*1*

Curcuma Longa (Turmeric) Root Extract

FOU = 177

Definition: Curcuma Longa (Turmeric) Root Extract is the extract of the roots of *Curcuma longa*.

***Reported* Functions**: Skin-Conditioning Agents - Miscellaneous

Notes: *(CAS No. 84775-52-0) The ingredients in this group are each derived from the same species.*

CIR draft grouping: (5 ingredients proposed with a total FOU = 220)	***FOU***
Curcuma Longa (Turmeric) Root Extract	*177*
Curcuma Longa (Turmeric) Root Oil	*17*
Curcuma Longa (Turmeric) Root Powder	*15*
Curcuma Longa (Turmeric) Rhizome Extract	*6*
Curcuma Longa (Turmeric) Leaf Extract	*5*

Lonicera Japonica (Honeysuckle) Flower Extract

FOU = 175

Definition: Lonicera Japonica (Honeysuckle) Flower Extract is the extract of the flowers of *Lonicera japonica.*

***Reported* Functions**: Skin-Conditioning Agents - Miscellaneous

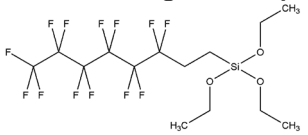
Notes: *(CAS No. 223749-79-9 (generic)) The ingredients in this group are each derived from the same species (also known as Japanese Honeysuckle).*

CIR draft grouping: (2 ingredients proposed with a total FOU = 180)	***FOU***
Lonicera Japonica (Honeysuckle) Flower Extract	*175*
Lonicera Japonica (Honeysuckle) Leaf Extract	*5*

Perfluorohexylethyl Triethoxysilane

FOU = 172

Definition: Perfluorohexylethyl Triethoxysilane is the organic compound that conforms to the structure:



***Reported* Functions**: Binders; Skin-Conditioning Agents - Miscellaneous

Notes: *(CAS No. 51851-37-7)*

Grouping proposal: None