ADMIN

Memo

Agenda

Minutes

EXPERT PANEL MEETING
June 16-17, 2022

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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: 161st Meeting of the Expert Panel — Thursday and Friday, June 16-17, 2022
Date: May 23, 2022

Welcome to the second Panel Meeting of 2022! The agenda and accompanying materials for the 161st Expert Panel Meeting, to be held on June 16-17, 2022, are now available. Please note that this meeting is on a ***Thursday and Friday***. The location is the ***same*** as in March – this meeting will be held virtually! Invitations (3 of them) 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/161st-expert-panel-meeting

The meeting agenda includes the consideration of 11 reports advancing in the review process, including 7 final reports, 3 tentative reports, and 1 draft report. Also on the agenda, are 7 rereview documents. Please note, this is the first time we have presented this format for rereviews. Considering the great number of rereviews on the Panel's docket, we have attempted to abbreviate this process for those reports wherein there might not be a need to reopen. ***Thus, in each case, the Panel is only being asked if the report should be reopened.*** Additionally, there are 5 administrative items: a draft resource document for utilizing GRAS determinations, a strategy memo regarding the potentially accelerated rereview of Kojic Acid, a strategy memo regarding the potentially accelerated rereview of Aluminum Hydroxide (and Alumina), a proposal to add certain prostaglandin analogues to the 2023 Priorities, and a proposal to make changes to the SOP for Use tables.

Hellos and goodbyes. As most of you are aware, Dr. Lisa Peterson retired from the Panel following the December 2021 meeting. However, we are now very happy to welcome world-class expert, Dr. Susan Tilton, to the Panel. Dr. Tilton brings a wealth of expertise in chemistry and toxicology, including specialized experience in bioinformatics, carcinogenicity, and inhalation toxicology. Nevertheless, Dr. Tilton has a prior commitment and will not be able to participate in Panel meetings until September 2022.


Dr. Susan Tilton


Dr. Allan Rettie

Two additional Panel members will retire before the end of 2022. In their stead, we are fortunate to have 2 world renowned experts joining us at this meeting, Drs. Allan Rettie and Dave Ross. Dr. Rettie brings expertise in chemistry and toxicology, with research interests in metabolism. Dr. Ross also brings expertise in chemistry and toxicology, with expertise in evaluating carcinogenic risk as a panel member of IARC.


Dr. Dave Ross

More information about these new additions, and all current Panel members, may be found at the Panel's membership page, https://ingredientsafetyexpertpanel.org/membership/.

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Team Meetings

Draft Report - There is 1 draft report for review. - Sufficient data to proceed, or issue an IDA?

1. Phytostearyl Glutamates – DR (Regina) – ***Dr. Belsito reports on day 2*** - This ingredient group includes the following 3 phytostearyl glutamates: Phytostearyl/Octyldodecyl Lauroyl Glutamate, Phytostearyl/Behenyl/Octyldodecyl Lauroyl Glutamate, and Phytostearyl/Behenyl/Octyldodecyl/Isostearyl Lauroyl Glutamate. The 3 phytostearyl glutamates are mixed esters that each comprise lauroyl glutamic acid esterified with a mixture of phytosterols and fatty alcohols.

According to 2022 FDA VCRP data, Phytostearyl/Octyldodecyl Lauroyl Glutamate has the greatest frequency of use; it is reported to be used in 325 cosmetic products, 311 of which are leave-on products and over a third of which are in lipstick formulations. The results of the concentration of use survey conducted by the Council in 2021 indicate that Phytostearyl/Behenyl/Octyldodecyl/Isostearyl Lauroyl Glutamate has the highest concentration of use; it is used at maximum use concentrations up to 25.6% in leave-on products (rouges). The maximum concentration of use reported for Phytostearyl/Octyldodecyl Lauroyl Glutamate is very similar; it is reported to be used at up to 25% in rouges and lipsticks.

Following an intensive search of information in the published scientific literature, online databases, and other sources on this ingredient, there was insufficient information found to justify the preparation of a formal Scientific Literature Review (SLR). Therefore, in October 2021, CIR issued an SLR Notice to Proceed (NTP) for Phytostearyl Glutamates, to alert interested parties that a safety assessment is being prepared and to request information in multiple areas, including:

- Chemistry information, including composition and structure, method of manufacture, and impurity data
- Toxicokinetics data relevant to routes of exposure expected with cosmetic use
- General toxicity data
- Developmental and reproductive toxicity data
- Genotoxicity data
- Carcinogenicity data
- Dermal irritation and sensitization data
- Inhalation toxicity data
- Any other relevant safety information that may be available

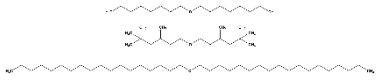
Since the issuing of the NTP, the following unpublished data have been received, and are included in this packet:

- Repeated insult patch test on a mixture containing 5.999% Phytostearyl/Octyldodecyl Lauroyl Glutamate
- Primary cutaneous tolerance - cytotoxicity study performed on an Episkin® reconstructed human epidermis model (test mixture containing 1% Phytostearyl/Octyldodecyl Lauroyl Glutamate)

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 Insufficient Data Announcement (IDA), specifying the data needs therein.

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

1. Fatty Ethers – TR (Preethi) – ***Dr. Belsito reports on day 2*** – This is the 2nd time the Panel is seeing a safety assessment of these 8 cosmetic ingredients. At the December 2021 meeting, a Draft Report was presented to the Panel. Upon review, the Panel issued an IDA for:



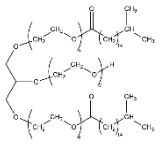
- Method of manufacture data (specific to cosmetic ingredient production) for Dicaprylyl Ether and Distearyl Ether

Data were not received in response to this IDA.

Updated (2022) VCRP data were received from the FDA and have been incorporated. No significant changes in reported use categories or frequencies occurred. Changes to the VCRP and changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review.

The Panel should carefully consider and discuss the data (or lack thereof), the draft Abstract, and draft Discussion presented in this report, and issue a tentative report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

2. Fatty Ester End-Capped Alkoxylates – TR (Christina) – ***Dr. Cohen reports on day 2*** – In December 2021, the Panel issued an IDA for these 14 fatty ester end-capped alkoxylates. The additional data needed to determine safety for these cosmetic ingredients were:



   - Use concentrations for PEG/PPG-8/3 Diisostearate
   - Method of manufacturing for all ingredients except PEG/PPG-8/3 Diisostearate
   - Composition and impurities data for all ingredients except PEG/PPG-8/3 Diisostearate

   Since the December meeting, CIR has received the maximum concentration of use data on PEG/PPG-8/3 Diisostearate. The Council reports that this ingredient is currently used at 5% in a leave-on hair conditioner. This ingredient was previously reported to be used at up to 59.9% in a face mask and mud pack, but these are no longer in production. In response to the Council survey, a supplier recommended a use concentration range of 1 - 10% for PEG/PPG-8/3 Diisostearate but did not include any use category information. No additional data were received.

   The Use Table has been updated with the 2022 VCRP survey data. According to 2022 data, the use of PEG/PPG-8/3 Diisostearate has decreased from 155 formulations to 98 formulations, with most uses reported in bath soaps and detergents. Use for PEG-12 decreased from 2 to 1 (hair tonic). No other changes were noted. There are 10 ingredients not reported to be in use, according to both the VCRP and the industry surveys. The new concentration of use and frequency, in addition to changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review.

   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 remain insufficient, the Panel should issue a tentative report with an insufficient data conclusion, specifying the data needs in the report Discussion.

3. Ginger – TR (Priya) – ***Dr. Cohen reports on day 2*** – At the December 2021 meeting, the Panel issued an IDA for these 9 ingredients. In order to determine the safety of these ingredients, the Panel requested the following data:

   - Method of manufacturing data on Zingiber Officinale (Ginger) Leaf Cell Extract
   - Composition and impurities data
     - if the composition of Zingiber Officinale (Ginger) Leaf Cell Extract notably differed from the composition of the remaining ginger ingredients, systemic toxicity data (28-d dermal toxicity, genotoxicity, developmental/reproductive toxicity, and/or carcinogenicity data) were also requested on Zingiber Officinale (Ginger) Leaf Cell Extract
   - Dermal irritation/sensitization data on Zingiber Officinale (Ginger) Extract at maximum concentrations of use

In addition, if available, the Panel requested information regarding the specific plant parts (e.g., leaves, rhizome) used in the preparation of the whole plant extract (Zingiber Officinale (Ginger) Extract). Since issuing the IDA, the following unpublished data have been received:

- Product specifications for a trade name mixture consisting of Ginger Officinale (Ginger) Root Extract (1 - 5%) and helianthus annus (sunflower) hybrid oil (> 50%)
- Composition information on *Zingiber officinale* (ginger) root
- Chemical/physical properties and specifications data on a trade name mixture consisting of Zingiber Officinale (Ginger) Water (98.5%) and phenoxyethanol (1.5%)
- Manufacturing, specifications, and composition/impurities data on a trade name mixture consisting of Zingiber Officinale (Ginger) Root Extract (≤ 1.5%), propylene glycol (68.5%), and water (30%)
- An HRIPT using a moisturizer containing 0.1% Zingiber Officinale (Ginger) Rhizome Extract (n = 54); negative results

In addition, changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review. 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, safe with qualifications, unsafe, insufficient data, or split conclusion should then be issued.

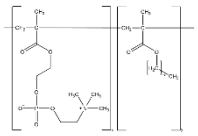
Draft Final Reports - There are 7 draft final reports for consideration. - Review these drafts, especially the rationales provided in the Discussion sections, and issue these as final reports, as appropriate.

1. Barley – FR (Christina) – ***Dr. Cohen reports on day 2*** – At the March 2022 meeting, the Panel issued a tentative report with the conclusion that the 5 barley seed- and sprout-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment. However, the Panel also concluded that the available data are insufficient to make a determination that the remaining 11 barley-derived ingredients are safe under the intended conditions of use in cosmetic formulations. The additional data needed to determine safety of these ingredients as used in cosmetics are:

   - Explanation of the plant parts used to make the whole plant extracts Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
   - Method of manufacturing for Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
   - Composition and impurities data for Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
   - 28-day dermal toxicity data on the whole plant extract Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
     - If positive, additional data, such as developmental and reproductive toxicity and genotoxicity data, may be needed
     - Alternatively, acceptable evidence of safe use as food for ingredients derived from the flower, leaf, stem, and root
   - Dermal irritation and sensitization data for Hordeum Leaf Extract, or other leaf ingredients

   Since the issuance of the tentative report, CIR has received no new unpublished data. Changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review. Comments that were received from the Council have been addressed. After carefully reviewing the Abstract, Discussion, and Conclusion, the Panel should be prepared to issue a final report.

2. Acryloyloxyethyl Phosphorylcholine – FR (Regina) – ***Dr. Cohen reports on day 2*** – At the December 2021 meeting, the Panel issued a tentative report for public comment with the conclusion that the acryloyloxyethyl phosphorylcholine polymer ingredients reviewed in the safety assessment are safe in cosmetics in the present practices of use and concentration.

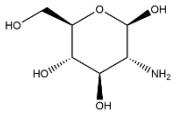


   Updated 2022 FDA VCRP data were received and incorporated into the report. These data were similar to 2021 FDA VCRP data, with negligible changes in the reported uses from the previous year.

Total reported uses of Polyquaternium-51 increased from 275 to 317 formulations, while Polyquaternium and Phosphorylcholine Glycol Acrylate use remained mostly the same. Changes reflecting updated VCRP data and newly added data are highlighted in yellow. Additionally, changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review.

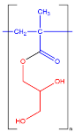
The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a final report.

3. Glucosamine – FR (Priya) – ***Dr. Cohen reports on day 2*** – At the March 2022 meeting, the Panel issued a tentative report for public comment on these 4 ingredients, with the conclusion that Acetyl Glucosamine, Glucosamine, Glucosamine HCl, and Glucosamine Sulfate are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.



Since the issuing of the tentative report, no new unpublished data were received. Changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review. The Panel should carefully consider the newly added data, the Abstract, Discussion, and Conclusion, and be prepared to issue a final report.

4. Glyceryl Acrylates – FR (Regina) – ***Dr. Belsito reports on day 2*** – At the March 2022 meeting, the Panel issued a tentative report for public comment with the conclusion that the 4 glyceryl acrylate ingredients reviewed in the safety assessment are safe in cosmetics in the present practices of use and concentration.



The Panel should carefully consider the Abstract, Discussion, and Conclusion, and be prepared to issue a final report.

5. Radish Root – FR (Preethi) – ***Dr. Belsito reports on day 2*** – At the December 2021 Panel meeting, the Panel issued a tentative report for public comment with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

Updated VCRP data were received and have been incorporated. Reported use categories and number of uses did not change significantly. Also, changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review. The Panel should carefully consider the Abstract, Discussion, and Conclusion, and be prepared to issue a final report.

6. Sage – FR (Preethi) – ***Dr. Cohen reports on day 2*** – At the December 2021 Panel meeting, the Panel issued a Tentative Report for public comment with the split conclusion that the following 6 leaf and oil ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Salvia Officinalis (Sage) Leaf
Salvia Officinalis (Sage) Leaf Extract
Salvia Officinalis (Sage) Leaf Oil
Salvia Officinalis (Sage) Leaf Powder
Salvia Officinalis (Sage) Leaf Water
Salvia Officinalis (Sage) Oil

However, the Panel also concluded that the available data are insufficient to make a determination that the remaining 6 Salvia officinalis (Sage)-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

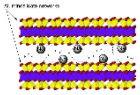
Salvia Officinalis (Sage) Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice
Salvia Officinalis (Sage) Flower/Leaf/Stem Water
Salvia Officinalis (Sage) Root Extract
Salvia Officinalis (Sage) Water

The data requested to satisfy the insufficiency are:

- 28-day dermal toxicity study for the Salvia Officinalis (Sage) Flower/Leaf/Stem Extract, Salvia Officinalis (Sage) Root Extract, or for the whole plant
    - depending on the results of the requested dermal study, additional toxicity data may be needed

No data were received in response to this request. Updated VCRP data were received and have been incorporated. Reported use categories and number of uses did not change significantly. Also, changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review. The Panel should carefully consider the Abstract, Discussion, and Conclusion, and be prepared to issue a final report.

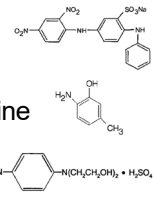
7. Zeolites – FAR (Christina) – ***Dr. Belsito reports on day 2*** – At the March 2022 meeting, the Panel issued a tentative amended report with the conclusion that the 6 zeolite ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.



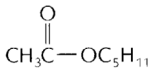
Since the issuance of the tentative amended Report, CIR has received no new unpublished data. Changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review. The Panel should carefully consider the Abstract, Discussion, and Conclusion, and be prepared to issue a final amended report.

Abbreviated Rereviews – There are 7 rereview documents – Please note, this is the first time we have presented this format for rereviews. Considering the significant number of rereviews on the Panel's docket, we have attempted to abbreviate this process for those reports wherein there might not be a need to reopen. In each case, the Panel is only being asked if the report should be reopened.

1. Hair Dyes – RR (Christina) – ***Dr. Belsito reports on day 2*** – Because it has been at least 15 years since these reports were published, in accord with CIR Procedures, the Panel should consider whether these safety assessments should be re-opened. Herein, you will find summarized information on Acid Orange 3, *N,N*-Bis(2-Hydroxyethyl)-*p*-Phenylenediamine Sulfate, and 6 cresol-related hair dyes (6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol). The Panel should carefully review the historical overview, comparison of original and new use data, the search strategy used, a synopsis of notable new data for each ingredient or ingredient group, and the use table. If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a draft amended report will be presented at an upcoming meeting.



2. Amyl Acetate – RR (Priya) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Amyl Acetate and Isoamyl Acetate in 1988, with the conclusion that these ingredients are safe in the present practices of use and concentration, as described in the safety assessment. Because it has been at least 15 years since the previous safety assessment was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of Amyl Acetate and Isoamyl Acetate should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1982 forward. A historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data were prepared.



New studies that were found as a result of the literature search include subchronic and developmental inhalation toxicity assays using Amyl Acetate, each yielding high NOAELs. Also found were genotoxicity assays using Isoamyl Acetate, each of which resulted in negative results. Two previous RIFM safety assessments reviewing Amyl Acetate and Isoamyl Acetate were also found. The Expert Panel for Fragrance Safety concluded that these ingredients are safe under the limits described in their safety assessments.

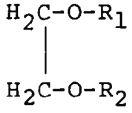
Also included for your review is a table of current and historical use data. The frequency and concentration

of use for Amyl Acetate has decreased from 18 to 4 uses, and from < 10% to ≤ 0.09%, respectively. In 1988, Isoamyl Acetate was not reported to be in use; however, according to 2022 FDA VCRP data, this ingredient is now used in 1 formulation (up to 0.22%). If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a draft amended report will be presented at an upcoming meeting.

3. Cottonseed – RR (Preethi) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Cottonseed Glyceride and Hydrogenated Cottonseed Glyceride, as part of a larger group of ingredients, in 2001, with the conclusion that these ingredients are safe as used in cosmetic products, as described in the safety assessment, provided that established and imposed limits on gossypol, heavy metals, and pesticide concentrations are not exceeded. (The 3 additional ingredients included in the 2001 assessment were subsequently included in the safety assessment of plant-derived fatty acid oils (2017), and are therefore not included in this re-review.)

   Because it has been at least 15 years since the safety assessment was published, in accordance with CIR Procedures, the Panel should consider whether the safety assessment of Cottonseed Glyceride and Hydrogenated Cottonseed Glyceride should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1996 forward. No relevant published data were found. If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a draft amended report will be presented at an upcoming meeting.

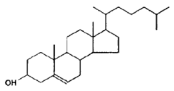
4. Glycol Stearates – RR (Regina) – ***Dr. Cohen reports on day 2*** – The Panel first published a review of the safety of Glycol Stearate and Glycol Stearate SE in 1982, with the conclusion that these ingredients are safe in the present practices of use and concentration, as described in that safety assessment. This conclusion was reaffirmed, as published in 2003. Glycol Distearate was included in the original report and 2003 re-review; however, because Glycol Distearate was included in the 2017 assessment of monoalkylglycol dialkyl acid esters, it is not being considered as part of this current re-review.



   Because it has been at least 15 years since the previous re-review was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of Glycol Stearate and Glycol Stearate SE should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1997 forward. No relevant published data were found.

   Since the initial re-review was considered, the frequency of use has increased for both ingredients. The maximum concentration of use for Glycol Stearate has decreased slightly, from 6% in 2001 to 5% in 2022. In 2001, Glycol Stearate SE was reported to be used at up to 12%; however, concentration of use data were not reported in 2022. If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a draft amended report will be presented at an upcoming meeting.

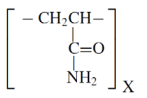
5. PEG Soy Sterols – RR (Priya) – ***Dr. Belsito reports on day 2*** – The Panel) first published a review of the safety of PEG Soy Sterol in 1996, with the conclusion that the data were insufficient to support the safety of this ingredient group. Subsequently, additional data were received, and in 2004, the Panel published a Final Amended Report with the conclusion that the 6 PEG Soy Sterol ingredients were safe as used in cosmetics, as described in the safety assessment.



   Because it has been at least 15 years since the final amended report was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of PEG Soy Sterols should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1998 forward. No relevant published data were found.

   Since the initial re-review was considered, the frequency of use has decreased for all ingredients that were reported to be in use, with the exception that PEG-30 Soy Sterol is now reported to be in use (11 uses). In 2000, the maximum concentration of use for this ingredient group was reported to be 2% in leave-on products for PEG-5 Soy Sterol, PEG-10 Soy Sterol, and PEG-25 Soy Sterol. Current concentration of use data (survey performed in 2020) indicate that PEG-10 Soy Sterol is used at up to 2.6% in rinse-off products, and up to 2.1% in leave-on products (in the category of tonics, dressings, and other hair grooming aids).

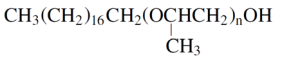
If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a draft amended report will be presented at an upcoming meeting.

6. Polyacrylamide – RR (Preethi) – ***Dr. Belsito reports on day 2*** – 
The Panel first published a review of the safety of Polyacrylamide in 1991, with the conclusion that with less than 0.01% acrylamide monomer content it is safe as used as described in the safety assessment. The Panel published a final amended report on the safety of Polyacrylamide, along with acrylamide monomer residues, in 2005. Although the Panel acknowledged that acrylamide is a demonstrated neurotoxin in humans and a carcinogen in animal tests, they also determined that neurotoxic levels would not be attained by the use of Polyacrylamide in cosmetics. Thus, the Panel concluded that Polyacrylamide is safe as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment, when the level of acrylamide monomer in formulation is not greater than 5 ppm.

   Because it has been at least 15 years since the final amended report was published, in accordance with CIR Procedures, the Panel should again consider whether the safety assessment of Polyacrylamide should be re-opened. An exhaustive search of the world's literature was performed for studies dated 2000 forward. No relevant new data were found.

   Generally, there has been an increase in frequency of use since the last review in 2005. In 2022, FDA VCRP data indicate that Polyacrylamide has 552 reported uses. Of note, reported use near the eye has increased from 2 in 2005 to 58 in 2022, although the reported concentration for this use category has not changed significantly. The maximum use concentration for this ingredient has remained essentially the same; in 2002, the maximum reported concentration of use was 2.8%, and in 2022, it is 3%. While use in baby products was not reported in 2005, 1 use in baby lotions, oils, powders, and creams, and a 2% use in other baby products, are reported in 2022.

   If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a draft amended report will be presented at an upcoming meeting.

7. PPG Stearyl Ethers – RR (Priya) – ***Dr. Belsito reports on day 2*** – 
The Panel first published a review of the safety of PPG-11 and PPG-15 Stearyl Ether in 2001, with the conclusion that these ingredients are safe as used in cosmetics, as described in the safety assessment. Because it has been at least 15 years since the previous safety assessment was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of PPG-11 and PPG-15 Stearyl Ether should be re-opened.

   An exhaustive search of the world's literature was performed from the year 1994 forward. A study was found evaluating the effect of PPG-15 Stearyl Ether (2.5, 5, and 10%) on the skin permeation of a psoriasis medication in pig ear skin. PPG-15 Stearyl Ether, at a concentration of 2.5%, resulted in notably increased skin permeation compared to isopropyl myristate, a common drug solvent. However, increasing concentrations of PPG-15 Stearyl Ether resulted in lower amounts of skin permeation, suggesting an inverse relationship between skin permeation enhancement and PPG-15 Stearyl Ether concentration.

   The frequencies of use of PPG-11 and PPG-15 Stearyl Ether have decreased since the original report was issued. Compared to 1998 concentration of use data, the maximum concentration of use of PPG-11 Stearyl Ether has decreased from 10% to 5%; however, the maximum concentration of use for PPG-15 Stearyl Ether has increased from 10 to 18%. If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a draft amended report will be presented at an upcoming meeting.

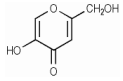
Administrative Items - there is 1 resource document (white paper), and 4 strategy memos.

1. GRAS– Admin – separate book – (Jinqiu) – ***Dr. Cohen reports on day 2*** – This is the first time the Panel is seeing this document. The document concisely introduces the FDA's current approach to the GRAS provision, with specific focus on its voluntary GRAS notification program. Notably, self-determination of GRAS status by manufacturers is allowed through the FDA's notification procedure. Under the GRAS notice inventory, FDA's opinion on the notified substance does not affirm the GRAS status under the

conditions of its intended use. Furthermore, FDA's response must be considered in context of the data available to reviewers at a point in time, because scientific knowledge and information about a particular ingredient can evolve over time. Therefore, when using GRAS status as a factor in the safety assessment of cosmetic ingredients, it should be considered with other relevant assessment factors that contribute to the determination of a safety margin, on a case-by-case basis.

The Panel is requested to review the draft white paper and determine whether the document represents their view on the recognition of GRAS status based on a voluntary self-affirming mechanism, as well as how to apply the supporting materials associated with GRAS notifications in the review process of cosmetic ingredient safety. ***The Panel should determine how, and to what extent, the document should be revised.***

2. Kojic Acid – SM (Bart) – ***Dr. Belsito reports on day 2*** – The Panel's safety assessment of Kojic Acid was published in the *International Journal of Toxicology* in 2010. Therein, the Panel concluded that the 2 end-points of concern, dermal sensitization and skin lightening, would not be seen at use concentrations below 1%; therefore, this ingredient is safe for use in cosmetic products up to that level. As a reminder, Kojic Acid is effective as a skin lightener; skin lightening is considered to be a drug effect in the US regulatory schema and is thus outside of the purview of this Panel.



The Panel also noted a large number of studies on the effects of Kojic Acid on rodent thyroid glands. The weight of evidence indicates differing factors, such as shorter plasma half-life of T4 in rodents and differences in transport and binding of protein for thyroid hormones between rodents and humans, allow the rodent thyroid system to be more likely to have a proliferative response to physical or chemical stimulation attributable to an indirect effect on thyroid hormone synthesis and secretion rather than a genotoxic mechanism. Recognizing that the rodent thyroid gland is sensitive to chemical substances and physiologic perturbations in ways different from that in humans, the Panel concluded that Kojic Acid would not pose a significant risk to human thyroid glands at the levels used in cosmetic products.

According to the standard 15-year rereview clock, the safety of this ingredient should be reconsidered in 2025. However, at the March meeting of the European Commission Scientific Committee on Consumer Safety (SCCS), Kojic Acid was deemed not safe when used as a skin lightening agent in cosmetic products at concentrations of up to 1%, due to concerns related to potential "endocrine disrupting" properties. In the SCCS's opinion, the use of Kojic Acid as a skin lightening agent in cosmetic products is safe for the consumer up to 0.7%.

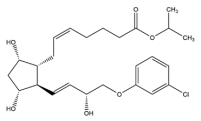
Would the Panel like to accelerate the rereview of Kojic Acid, or wait out the 15-year clock?

3. Aluminum Hydroxide (AlOH) – SM – (Bart) – ***Dr. Cohen reports on day 2*** – This year, the American Contact Dermatitis Society (ACDS) selected aluminum as the "Allergen of the Year." Further in that selection documentation, Aluminum Hydroxide is identified as the primary cause for such allergic reactions. In 2016, the Panel's safety assessment of Alumina and Aluminum Hydroxide was published in the *International Journal of Toxicology*. Therein, the Panel concluded that Alumina and Aluminum Hydroxide are safe in the present practices of use and concentration described in that safety assessment.

Accordingly, Alumina and Aluminum Hydroxide are not due for rereview, based on the procedural 15-year clock, until 2031. However, if the Panel would like to reconsider the safety of these ingredients earlier, in light of the potential allergenicity, the timing of such reassessment may be accelerated. If the Panel chooses to accelerate the rereview of these ingredients, the addition of Aluminum Chloride may also be considered. While Aluminum Chloride currently only has 3 reported uses, inclusion in the rereview may be useful as this ingredient is a known potent allergen; indeed, it is the chemical of choice for patch testing when aluminum sensitivity is suspected (commonly referred to as aluminum chloride hexahydrate (ACH)).

Would the Panel like to accelerate the rereview of Alumina and Aluminum Hydroxide? If yes, would the Panel like to include Aluminum Chloride in that rereview?

4. Prostaglandins – SM (Bart) – ***Dr. Belsito reports on day 2*** – At the March meeting this year, 4 prostaglandin analogues were proposed for inclusion in the 2023 Priorities, due in part to the actions of the SCCS. At that meeting of the Panel, representatives from the FDA were requested to evaluate whether the safety evaluation of prostaglandin ingredients is exclusively within the purview of FDA Drugs, or if the use of such ingredients could be



considered within cosmetic use.

Since the March meeting, CIR has received communications from representatives at the FDA. Therein, the jurisdictional issues (drug vs. cosmetic) were discussed and determined to be based on the claims, such that if growth (or other drug claims) are made, products would be considered drugs, and manufacturers would be required to follow drug requirements to market the products. In the absence of such claims, however, the intended use of such products as drugs, regardless of ingredients, could not be established and those products would be considered to be cosmetics. Representatives from OCAC and CDER have reviewed the website of at least one prostaglandin-containing product which does not appear to make drug claims. As a result, it would ***not*** be expected that such a product would be registered as a drug. Instead, however, such a product could be registered in the VCRP, as a cosmetic.

Accordingly, the Panel is once again asked to consider certain prostaglandin analogue ingredients for inclusion on the 2023 Priorities List. The 4 ingredients proposed at the March meeting, in addition to all other prostaglandin analogues and other eyelash conditioning agent ingredients listed in the Dictionary, are provided for prioritization consideration. While only Isopropyl Cloprostenate currently has reported uses (FOU = 3) in the VCRP, please consider that additional uses (for this ingredient and others) may yet be unreported because of the perceived ambiguity in jurisdiction (i.e., drug vs. cosmetic).

5. Use Tables – SM (Monice) – ***Dr. Cohen reports on day 2*** – For the past 10+ years, CIR reports have included Use Tables that comprise a format in which the frequency and concentration of use for each ingredient is summarized by duration (e.g., leave-on, rinse-off) and type (e.g., eye area, incidental inhalation, etc.) of exposure. The product use categories for each ingredient is ascribed to, as reported in the VCRP and as a result of the Council survey, are used to develop the table, as described on the CIR website (https://www.cir-safety.org/cir-findings).

   When CIR staff developed the current format, it was done to assist the Panel's review of use of each ingredient. Prior to that development, the safety assessments often included a very large number of ingredients, with all product categories that were in use identified, and consequently, review of the Use Tables could be cumbersome. Therefore, a summarized format was developed. Also at that time, the duration, route, and areas of exposure were more discernable. However, it is becoming readily apparent that is no longer true. For example, shampoos, which were assumed to be liquid rinse-off formulations, can now be spray leave-on formulations. Nevertheless, the only information available via the VCRP product categories is the generic designation "shampoo."

   Because CIR reports now tend to include a much smaller number of ingredients, and because of the uncertainty as to how an ingredient is being used, ***CIR is asking the Panel if it is their preference to utilize a different format for the Use Table.*** The proposal being put forth is a Use Table that identifies each product category that has reported frequency and concentration of use data, much like what was done in the past.

Full Panel Meeting

The Panel will consider the 7 reports to be issued as final safety assessments, followed by the remaining reports advancing in the process (including the tentative reports and a draft report). In addition, a consensus should be reached for the 7 rereview documents, the 1 resource document, 4 strategy memos.

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

Looking forward to seeing you all (virtually)!

Agenda
161st Meeting of the Expert Panel for Cosmetic Ingredient Safety
June 16th - 17th, 2022

Virtual via Microsoft Teams

Thursday, June 16th

8:30 AM	**WELCOME TO THE 161st EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:45 AM	**TEAM MEETINGS**	**Drs. Cohen/Belsito**

Dr. Cohen's Team*		**Dr. Belsito's Team**	
FAR (CB)	Zeolites	Admin (JZ)	GRAS
FR (CB)	Barley	FR (PR)	Sage
TR (CB)	Fatty Ester Alkoxylates	FR (PR)	Radish
RR (CB|BH)	Hair Dyes	TR (PR)	Fatty Ethers
RR (RT|BH)	Glycol Stearates	RR (PR|MF)	Polyacrylamide
FR (RT)	Acryloyloxyethyl Phosphorylcholine	RR (PR|MF)	Cottonseed
FR (RT)	Glyceryl Acrylates	RR (PC|MF)	PPG Stearyl Ethers
DR (RT)	Phytostearyl Glutamates	RR (PC|MF)	Amyl Acetates
SM (BH)	Kojic Acid / AlOH / Prostaglandins / Use	RR (PC|MF)	PEGs Soy Sterol
FR (PR)	Sage	FR (PC)	Glucosamine
FR (PR)	Radish	TR (PC)	Ginger
TR (PR)	Fatty Ethers	SM (MF)	Kojic Acid / AlOH / Prostaglandins / Use
RR (PR|BH)	Polyacrylamide	FAR (CB)	Zeolites
RR (PR|BH)	Cottonseed	FR (CB)	Barley
RR (PC|BH)	PPG Stearyl Ethers	TR (CB)	Fatty Ester Alkoxylates
RR (PC|BH)	Amyl Acetates	RR (CB|BH)	Hair Dyes
RR (PC|BH)	PEGs Soy Sterol	RR (RT|BH)	Glycol Stearates
FR (PC)	Glucosamine	FR (RT)	Acryloyloxyethyl Phosphorylcholine
TR (PC)	Ginger	FR (RT)	Glyceryl Acrylates
Admin (JZ)	GRAS	DR (RT)	Phytostearyl Glutamates

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

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

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

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

Cosmetic Ingredient Review

Friday, June 17th			
8:30 AM	**WELCOME TO THE 161st FULL EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:40 AM	Admin	**MINUTES OF THE MARCH 2022 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 AM	**DIRECTOR'S REPORT**		**Dr. Heldreth**
9:10 AM	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**		

Final Reports

FR (CB)	Barley-Derived Ingredients – ***Dr. Cohen reports***
FAR (CB)	Zeolites – ***Dr. Belsito reports***
FR (RT)	Acryloyloxyethyl Phosphorylcholine – ***Dr. Cohen reports***
FR (RT)	Glyceryl Acrylates – ***Dr. Belsito reports***
FR (PC)	Glucosamine Ingredients – ***Dr. Cohen reports***
FR (PR)	Radish Root Derived-Ingredients – ***Dr. Belsito reports***
FR (PR)	Sage - *Salvia officinalis*-Derived Ingredients – ***Dr. Cohen reports***

Reports Advancing

TR (PR)	Fatty Ethers (Dicaprylyl Ether) – ***Dr. Belsito reports***
TR (CB)	Fatty Ester End-Capped Alkoxylates – ***Dr. Cohen reports***
DR (RT)	Phytostearyl Glutamates – ***Dr. Belsito reports***
TR (PC)	Ginger - *Zingiber officinale* Ingredients – ***Dr. Cohen Reports***

Other Items

RR (CB|BH|MF)	Hair Dyes – ***Dr. Belsito reports***
RR (RT|MF|BH)	Glycol Stearates – ***Dr. Cohen reports***
RR (PR|BH|MF)	Polyacrylamide – ***Dr. Belsito reports***
RR (PR|MF|BH)	Cottonseed – ***Dr. Cohen reports***
RR (PC|BH|MF)	PPG Stearyl Ethers – ***Dr. Belsito reports***
RR (PC|MF|BH)	Amyl Acetates – ***Dr. Cohen reports***
RR (PC|BH|MF)	PEGs Soy Sterol – ***Dr. Belsito reports***
Admin (JZ)	Food Use - GRAS Resource Document – ***Dr. Cohen reports***
SM (BH)	Kojic Acid – ***Dr. Belsito reports***
SM (BH)	Aluminum Hydroxide (AlOH) – ***Dr. Cohen reports***
SM (BH)	Prostaglandins – ***Dr. Belsito reports***
SM (MF)	Use Tables – ***Dr. Cohen reports***

ADJOURN - *Next meeting Monday and Tuesday, **September 26-27, 2022**, will also be held virtually. Please check the CIR website for details as the meeting approaches.*

On the basis of all data and information submitted, and after following all of the Procedures (https://www.cir-safety.org/supplementaldoc/cir-procedures), the Expert Panel shall determine whether each ingredient, under each relevant condition of use, is safe, safe with qualifications, unsafe, or there are insufficient data or information to make a determination of safety. Upon making such a determination, the Expert Panel shall issue a conclusion and/or announcement.

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

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ONE HUNDRED SIXTIETH MEETING

OF THE

EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

March 7-8, 2022

Microsoft Teams Virtual Meeting

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairperson

Donald V. Belsito, M.D., Teamleader

David E. Cohen, M.D., Teamleader

Curtis D. Klaassen, Ph.D.

Daniel C. Liebler, Ph.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

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

Liaison Representatives

Consumer

Thomas Gremillion, J.D.

Industry

Alex Kowcz, M.B.A.

Government

Prashiela Manga, 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 - Toxicologist

Analysis
Christina L. Burnett, MSES - Senior Scientific Analyst

Priya Cherian - Senior Scientific Analyst

Preethi S. Raj, MS - Senior Scientific Analyst

Regina Tucker –Scientific Analyst

Information Services
Kevin Stone Fries, MLS - Information Services Manager

Other Meeting Attendees

Name	***Organization***
Asma Abbas	Beesline International SAL
Irina Agro	Ashland
Nosheen Ahmad	Mary Kay, Inc.
Jay Ansell	Personal Care Products Council
Michelle Barsoum	Botanic Innovatins, LLC
Don Bjerke	Procter & Gamble
Richard Brown	Wyo-Ben, Inc.
Roshil Budhram	Masts
Jens Burfeindt	IKW e.V., Germany
Sophia Chen	Sandream Impact
Anne Corriou	Givaudan
Vivek Dadhania	Bath & Body Works
Carol Eisenmann	Personal Care Products Council
Emily Gupta	unidentified
Sara Farahmand	Edgewell Personal Care
Christine Mazza Ferreira	unidentified
James Flanagan	Coty, Inc.
Karine Ghalayini	Beesline International SAL
Katie Gibbs	Cardno ChemRisk
Jessica Gray	KaMin LLC
Marita Grothus	IKW
Jörg Herbst	NCMA Consulting
Doug Hoffman	KaMin LLC
Kurt Hsiung	unidentified
Birgit Huber	IKW
Claudia Jackson	Carma Laboratories, Inc.
Jacobla	unidentified
Sandra James-Yi	Nu Skin Enterprises
Brett Jurd	W.R. Grace
Martha Elena Leal	Mary Kay, Inc.
Linda Loretz	Personal Care Products Council
David Lysy	unidentified
Maxwell Mangrum	KaMin LLC
Rola Masrieh	Beesline International SAL
Michael Maynard	Beiersdorf
Tim McCraw	Skin Science Advisors, LLC
Wilmelys Mendez	International Flavors & Fragrances, Inc.
Demetrius Michos	W.R. Grace
Kris Miles	Nouryon
Bhashkar Mukerji	Givaudan
Brooke Murray	unidentified
Shanti Pabbathi	unidentified
Jillian Parker	Cardno ChemRisk
Mary Parker	unidentified
Damni Parran	Nouryon Chemicals, LLC
Phillip Prather	ATTIA
Meche Ragland	KDC/One Columbus
Klaus Rettinger	IKW
rroper	unidentified
Alexandra Gorman Scranton	Women's Voices for the Earth
Amrita Sivia	UC Davis
Ingrid Tatar	unidentified
Suzana Theophilus	Edgewell Personal Care
Larissa Walker	MatTek Corp.
Brian Wall	Colgate-Palmolive
Lisa Wiseman	Kolmar Laboratories, Inc.
Carina Woodruff	UCSF Health
Gloria Zuclich	Keystone Industries

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 160th meeting of the Expert Panel for Cosmetic Ingredient Safety. She announced the resignation of Dr. Lisa Peterson from the Panel. The CIR Steering Committee will be filling her position soon, possibly with an expert in specialty fields such as inhalation.

Dr. Bergfeld thanked Dr. Bjerke for the presentation on alternative methods for the assessment of contact dermatitis. The Panel always appreciates being apprised on the latest research methodologies. Dr. Bergfeld also expressed her appreciation towards CIR staff for all their continuing efforts and research.

Dr. Bergfeld noted that comments were received from the CIR Scientific and Support Committee and Women's Voices of the Earth, including comments on airbrush technology. The Panel will continue its review of the airbrush and inhalation statements used in safety assessments. Dr. Bergfeld stated that Dr. Heldreth had communicated with the US FDA and the US Consumer Product Safety Commission regarding regulations that apply to airbrush use in cosmetics. Currently there is no clear answer as to who is responsible for the safety of the use of this technology for cosmetic application.

Dr. Bergfeld stated that the Panel would review 15 ingredient reports, including 4 final reports, 7 tentative reports, and 4 draft reports. Four of the 15 reports are on botanical ingredients. Additionally, the Panel was to review the priority list for 2023, the reorganization of yeast ingredients, and the re-review summaries of 2 ingredient groups. With regards to the priority list, and especially with botanical ingredients, Dr. Bergfeld encouraged Industry to provide data to CIR and the Expert Panel for Cosmetic Ingredient Safety as quickly as possible so that ingredients could be reviewed thoroughly and expeditiously.

APPROVAL OF MINUTES

The minutes of the December 6-7, 2021 (159th) Expert Panel meeting were approved. Editorial comments were provided by Drs. Belsito and Shank.

DIRECTOR'S REPORT

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the CIR program. With the conclusion of the December meeting, the Panel determined the safety of almost 6,000 ingredients since its conception in 1976. He noted that, sadly, Dr. Lisa Peterson retired from the Panel. A meeting of the CIR Steering Committee is scheduled for the following week to vote on nominees to fill the vacancy. Accordingly, Dr. Heldreth requested that candidates be nominated as soon as possible. Nominees need not be chemists, as there have been multiple proposals to instead supplement the Panel's expertise with backgrounds in new alternative methods, inhalation toxicology, and the like.

FINAL SAFETY ASSESSMENTS

Acrylamide/Acrylate Copolymers
The Expert Panel for Cosmetic Ingredient Safety (Panel) issued a Final Report with the conclusion that the following 16 acrylamide/acrylate copolymer ingredients are safe as used in cosmetics in the present practices of use and concentrations as described in the safety assessment.

Acrylamide/Ammonium Acrylate Copolymer
Acrylamide/Sodium Acrylate Copolymer
Acrylates/Acrylamide Copolymer
Acrylates/t-Butylacrylamide Copolymer
Acrylates/Methacrylamide Copolymer
Acrylates/Octylacrylamide Copolymer
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer*
t-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer*
Butyl Acrylate/Isopropylacrylamide/PEG-18 Dimethacrylate Crosspolymer*
Corn Starch/Acrylamide/Sodium Acrylate Copolymer
Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Dimethylacrylamide/Lauryl Methacrylate Copolymer
Potassium Acrylates/Acrylamide Copolymer*
Sodium Acrylate/Hydroxyethyl Acrylamide Copolymer*
Starch/Acrylates/Acrylamide Copolymer*

**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.*

Formulators of these ingredients should ensure that the final monomer concentrations do not exceed 5 ppm. The Panel was made aware of the use of Acrylates/Octylacrylamide Copolymer in airbrush devices from sources outside of the FDA's Voluntary Cosmetic Registration Program (VCRP) and concentration survey processes conducted by the Personal Care Product Council (Council). The Panel determined that there were insufficient data to conclude on the safety of these acrylamide/acrylate copolymer ingredients when used in airbrush devices.

Methicones

The Panel issued a Final Amended Report with a split conclusion for these 30 ingredients. Specifically, the Panel concluded that these ingredients are safe as used in cosmetics in the present practices of use and concentration as described in the report when formulated to be non-irritating, with the exception that the data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled when applied using airbrush devices.

Amino Bispropyl Dimethicone
Aminopropyl Dimethicone
Amodimethicone
Amodimethicone Hydroxystearate*
Behenoxy Dimethicone
C20-24 Alkyl Dimethicone
C20-24 Alkyl Methicone*
C24-28 Alkyl Dimethicone*
C24-28 Alkyl Methicone
C26-28 Alkyl Dimethicone

C26-28 Alkyl Methicone*
C30-45 Alkyl Dimethicone
C30-45 Alkyl Methicone
C30-60 Alkyl Dimethicone
C32 Alkyl Dimethicone*
Capryl Dimethicone
Caprylyl Methicone
Cetearyl Methicone
Cetyl Dimethicone
Dimethicone
Dimethoxysilyl Ethylenediaminopropyl Dimethicone
Hexyl Dimethicone
Hexyl Methicone*
Hydroxypropyldimethicone*
Methicone
Stearamidopropyl Dimethicone*
Stearoxy Dimethicone
Stearyl Dimethicone
Stearyl Methicone
Vinyl Dimethicone

**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 agreed that methods of use, including concentration of use and exposure duration and frequency, for these ingredients in products applied using airbrush devices are still lacking. Particle size distribution, as well as additional data, are still needed to make a determination of safety for the use of these ingredients in products delivered via airbrush technology. Additional data needs include information on the regulation of spray, or other, delivery systems for cosmetics applied via airbrush technology; and methods of use, including concentration of use and exposure duration and frequency, for all cosmetics applied via airbrush technology. Thus, the Panel deemed the available data insufficient to make a determination of safety for this product category.

Rosa damascena

The Panel issued a Final Report with the conclusion that the following 10 ingredients are safe as used in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

Hydrolyzed Rosa Damascena Flower Extract*
Rosa Damascena Bud Extract*
Rosa Damascena Extract
Rosa Damascena Flower
Rosa Damascena Flower Extract
Rosa Damascena Flower Oil
Rosa Damascena Flower Powder
Rosa Damascena Flower Water
Rosa Damascena Flower Water Extract
Rosa Damascena Flower Wax

**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 acknowledged the presence of potentially sensitizing constituents in the composition of these ingredients; accordingly, the Panel stated that because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. According to 2022 VCRP data, Rosa Damascena Flower Water has 302 reported uses, Rosa Damascena Flower Extract has 293 reported uses, and Rosa Damascena Flower Oil has 229 reported uses. Additionally, updated results from the 2019 Council survey also indicate that the highest reported maximum use concentration for these ingredients (Rosa Damascena Flower Oil at up to 10.8% in other skincare preparations) is an essential oil which is sold with instructions to dilute before use; the second highest reported concentration of use is for Rosa Damascena Flower Water, at up to 1.9% in foundations.

Ubiquinone

The Panel issued a Final Report with the conclusion that the following 4 ingredients are safe as used in cosmetics in the present practices of use and concentrations described in the safety assessment. The safety of these ingredients was supported by the available oral toxicity, developmental and reproductive toxicity, genotoxicity, carcinogenicity, and irritation/sensitization data, as well as by the natural presence of ubiquinone in the body and widespread use as a dietary supplement.

Disodium Ubiquinone Hydroxydecyl Ubiquinone* Ubiquinol Ubiquinone

**Concentrations of use were not reported. Were this ingredient found to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to the other ingredients.*

According to 2022 VCRP data, Ubiquinone, is reported to be used in 221 formulations (208 of which are leave-on formulations). Results from concentration of use surveys, conducted by Council in f2018 and 2020, indicate that Ubiquinone also has the highest reported concentration of use, at up to 0.05% in body and hand products.

TENTATIVE SAFETY ASSESSMENTS

Barley

The Panel issued a Tentative Report for public comment with the conclusion that the following 5 barley-derived ingredients are safe as used in cosmetics in the present practices of use and concentrations described in this safety assessment:

Hordeum Distichon (Barley) Seed Flour*
Hordeum Vulgare Seed Extract
Hordeum Vulgare Seed Flour
Hordeum Vulgare Seed Water*
Hordeum Vulgare Sprout Extract*

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

The Panel noted that the barley seed- and sprout-derived ingredients that are reviewed in this safety assessment are found in foods that are consumed daily, and daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. The potential for systemic exposure from the absorption of these ingredients through the skin is much less than the potential for systemic exposure from absorption through oral exposures. This fact, coupled with negative findings in human dermal irritation and sensitization studies on whole plant extracts and seed extracts, led the Panel to determine that barley seed- and sprout-derived ingredients are safe for use in cosmetic products.

However, the Panel also concluded that the available data are insufficient to make a determination of safety on the following 11 barley-derived ingredients:

Hordeum Distichon (Barley) Extract
Hordeum Vulgare Extract
Hordeum Vulgare Flower/Leaf/Stem Juice**
Hordeum Vulgare Juice**
Hordeum Vulgare Leaf Extract
Hordeum Vulgare Leaf Juice
Hordeum Vulgare Leaf Powder**
Hordeum Vulgare Leaf/Stem Powder**
Hordeum Vulgare Powder**
Hordeum Vulgare Root Extract
Hordeum Vulgare Stem Water**

***There are currently no uses reported for these ingredients.*

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

- Explanation of the plant parts used to make the whole plant extracts Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
- Method of manufacturing for Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
- Composition and impurities data for Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
- 28-day dermal toxicity data on the whole plant extract Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract
    - If positive, additional data, such as developmental and reproductive toxicity and genotoxicity data, may be needed
    - Alternatively, acceptable evidence of safe use as food for ingredients derived from the flower, leaf, stem, and root
- Dermal irritation and sensitization data for Hordeum Leaf Extract, or other leaf ingredients

Diatomaceous Earth

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

Glucosamine

The Panel issued a Tentative Report for public comment with the conclusion that Acetyl Glucosamine, Glucosamine, Glucosamine HCl, and Glucosamine Sulfate* are safe as used in cosmetics in the present practices of use and concentration, when formulated to be non-irritating. The Panel noted the mild cumulative irritation during the induction phase of a human repeat insult patch test (HRIPT) evaluating an eye lotion containing 2% Acetyl Glucosamine. Because this irritation was observed at a concentration of 2%, and the maximum concentration of use of Acetyl Glucosamine in cosmetics is reported to be 5%, formulators should ensure that products containing these glucosamine ingredients are formulated to be non-irritating. In addition, the Panel considered the lack of human sensitization data at the maximum use concentration of 5%; however, the available in vitro and in vivo sensitization data coupled with the Panel's clinical experience and a lack of sensitization case reports, mitigated this concern. The safety of these ingredients is further supported by their use as dietary supplements/debulking agents, and the available systemic toxicity data.

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

Glyceryl Acrylates

The Panel issued a Tentative Report for public comment with the conclusion that the Caprylyl Glycol/Glycerin/Polyacrylic Acid Copolymer, Glyceryl Acrylate/Acrylic Acid Copolymer, Glyceryl Polyacrylate, and Glyceryl Polymethacrylate are safe as used in cosmetics in the present practices of use and concentrations described in the safety assessment. The Panel determined that the available data were sufficient to support the safety of all 4 glyceryl acrylates. Representative data on method of manufacturing and impurities were adequate for evaluating the entire group of ingredients. Safety was further supported by the large molecular weights of these ingredients. Glyceryl Polyacrylate, for example, has a molecular weight greater than 500,000 Da. The other polymers are also very large, which precludes dermal absorption.

Glycolactones

The Panel issued a Tentative Report for public comment with the conclusion that Gluconolactone is safe as used in cosmetics in the present practices of use and concentration as described in the safety assessment. The Panel also concluded that the available data are insufficient to make a determination that the remaining ingredients (i.e., Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone, none of which are reported to be in use) are safe under the intended conditions of use in cosmetic formulations. To conclude on the safety of Glucarolactone, and Glucoheptonolactone, the Panel requires impurities and cosmetic-specific method of manufacturing data. In addition, impurities data are required to determine the safety of Galactonolactone and Ribonolactone.

Hydroxyacetophenone

The Panel issued a Tentative Report for public comment with the conclusion that this ingredient is safe as used in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel noted that Hydroxyacetophenone is conferred a generally recognized as safe (GRAS) status as a food flavoring substance by the Flavoring, Extract, and Manufacturing Association (FEMA). Additionally, the Panel noted reported purity of 99.5%, low concentrations of use in cosmetics, a favorable toxicological profile, and lack of chemical structure alerts for this ingredient; the Panel agreed that these considerations mitigated systemic toxicity concerns. The Panel noted positive ocular irritation data and considered that the ingredient was tested undiluted and at a much higher concentration than possible based the reported maximum use concentration near the eye, at up to 0.23% in eye lotions and eye makeup removers. Hence, the Panel stated that manufacturers should be aware of the potential for ocular irritation and assure that these products are formulated to be non-irritating.

Portulaca oleracea

The Panel issued a Tentative Report for public comment with the conclusion that the following 4 *Portulaca oleracea*-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Portulaca Oleracea Extract
Portulaca Oleracea Flower/Leaf/Stem Extract*
Portulaca Oleracea Juice*
Portulaca Oleracea Water

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

After reviewing scientific literature that confirmed the use of the whole *Portulaca oleracea* plant as a food, the Panel's previous concerns regarding systemic toxicity were mitigated. The potential for systemic exposure from the absorption of these ingredients through the skin is much less than the potential for systemic exposure from absorption through consumption. This fact, coupled with negative findings in human dermal irritation and sensitization studies on the whole plant extract, led the Panel to determine that *Portulaca oleracea*-derived ingredients are safe for use in cosmetic products. The Panel identified the presence of potentially sensitizing constituents in the composition of these ingredients; accordingly, the Panel stated that because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers.

Starch Phosphates

The Panel issued a Tentative Report for public comment with the conclusion that these 4 starch phosphates are safe as used in cosmetics in the present practices of use and concentration described in the safety assessment.

Distarch Phosphate
Distarch Phosphate Acetate*
Hydroxypropyl Starch Phosphate
Sodium Hydroxypropyl Starch Phosphate

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

The Panel removed Sodium Dimaltodextrin Phosphate from the ingredient list. The Panel concluded that even though Sodium Dimaltodextrin Phosphate is made from the same monomer (α 1-4 glucose), the polymerized chains of this molecule are much shorter than the other ingredients in this report; therefore, Sodium Dimaltodextrin Phosphate is chemically different from the other ingredients, including being freely water soluble.

Zeolites

The Panel issued a Tentative Amended Report for public comment with the conclusion that the following 6 zeolite ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Ammonium Silver Zeolite*
Gold Zeolite*
Silver Copper Zeolite*
Titanium Zeolite*
Zeolite
Zinc Zeolite

**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 erionite is a naturally occurring fibrous material that is carcinogenic to humans and animals and is significantly more structurally similar to asbestos than the zeolite ingredients discussed in this report (i.e., the superstructures of the zeolites in this report comprise layered sheets, while erionite (and by comparison, asbestos) is fibrous). The Panel also expressed concern about the presence of heavy metals and free metal ions in zeolite ingredients. The metals in Ammonium Silver Zeolite, Gold Zeolite, Silver Copper Zeolite, Titanium Zeolite, and Zinc Zeolite are unavailable (i.e., not easily released) due to the nature of the zeolite framework. The zeolites are also not likely to absorb through the skin. Although other heavy metals may be present during mining, those should be readily avoidable/separable. Accordingly, the Panel stressed that the cosmetics industry should continue to use current good manufacturing processes (cGMPs) to ensure erionite and available heavy metals are not present in cosmetic formulations.

INSUFFICIENT DATA ANNOUNCEMENTS

Clays

The Panel issued an Insufficient Data Announcement (IDA) for these 7 clay ingredients.

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

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

- Particle size distribution (mean and range) on all ingredients, except Bentonite
- Chronic inhalation data on all ingredients, except Attapulgite and Kaolin
- Human dermal irritation and sensitization data at maximum use concentrations

Rosa centifolia

The Panel issued an IDA for these 12 *Rosa centifolia*-derived ingredients.

Rosa Centifolia Bud Extract
Rosa Centifolia Callus Culture Extract
Rosa Centifolia Extract
Rosa Centifolia Flower
Rosa Centifolia Flower Extract
Rosa Centifolia Flower Juice
Rosa Centifolia Flower Oil
Rosa Centifolia Flower Powder
Rosa Centifolia Flower Water
Rosa Centifolia Flower Wax
Rosa Centifolia Leaf Cell Extract
Rosa Centifolia Stem Extract

The additional data needed to determine safety for these cosmetic ingredients and address data insufficiencies include:

- Method of manufacturing
- Composition and impurities data for all, except the flower and bud ingredients
- Dermal toxicity (28-day dermal)
    - If positive, other toxicological endpoints (e.g., developmental and reproductive toxicity, genotoxicity, carcinogenicity, etc.) may be needed

ADDITIONAL PANEL DELIBERATIONS

Presentation

Additionally, Dr. Don Bjerke, of the Proctor & Gamble company and also the chair of the CIR Science and Support Committee, provided a very informative presentation, "Skin Sensitization Next Generation Risk Assessment Framework and Case Study." The presentation detailed vetted, alternative tests and strategies to assessing the skin sensitization potential of cosmetic ingredients. The presentation is available on the meeting page, https://www.cir-safety.org/sites/default/files/160th%20CIR%20EP%20Skin%20Sensitization%20NAM%20Upate%20Don%20Bjerke%20Final%20updated.pdf.

Methacrylate Ester Monomers – Rereview Summary

The Panel determined that the published final report on methacrylate ester monomers should not be reopened and that the original conclusion on these ingredients remains valid. It was agreed that an updated search of the published literature did not reveal toxicity data that warrant re-evaluation of the safety of these ingredients in cosmetic products. The Panel affirmed the written summary as presented.

2023 Draft Priorities

The CIR Procedures require preparation of the 2023 Draft Priority List for public comment by June 1, 2022. However, it is advantageous for the 2023 Draft Priority List to be issued for public comment earlier (March 2022) in the process to allow more time for the acquisition of data. The priority list is typically based on stakeholder requests (e.g., a hair dye) and frequency of use (FOU) data from FDA's VCRP; this year, VCRP data were received from the FDA on January 11 (in response to a Freedom of Information Act request).

While the list below includes only the lead ingredients, groupings of ingredients, drafted by CIR Staff, can be found in the Panel meeting book (https://www.cir-safety.org/sites/default/files/Admin_Priorities.pdf). There are 15 reports proposed, covering 60 ingredients, on the 2023 Draft Priorities List (2 of the ingredients on this list are proposed to be grouped together in 1 report). Once a proposal of a hair dye for assessment has been received from the PCPC Hair Color Technical Committee, 16 new reports in total will be proposed for the 2023 docket. Reports previously prioritized and on the CIR docket at the end of 2022, as well as an extensive number of re-reviews of previous assessments, will supplement the total number of reports to be assessed in 2023.

Information was provided that certain prostaglandins analogs might be in use in cosmetics. However, the Panel agrees that such is the purview of the FDA, as these are known drug uses. Thus, the proposed priorities for 2023 are:

Ingredients	Frequency of Use (FOU) Data Year 2022
For cause	
***To be determined* – a hair dye**	**-**
Per FOU	
Sodium Hydrosulfite	**246**
Pelargonium Graveolens Flower Oil	**236**
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	**234**
Diglycerin	**211**
Polyglycerin-3	**208**
Sigesbeckia Orientalis Extract	**202**
Houttuynia Cordata Extract	**201**
Malva Sylvestris (Mallow) Extract	**198**
Palmitoyl Pentapeptide-4	**198**
Salix Alba (Willow) Bark Extract	**197**
Centaurea Cyanus Flower Extract	**196**
Lactobacillus Ferment	**196**
Copper Gluconate	**192**
Inositol	**190**
Paeonia Suffruticosa Root Extract	**189**
Nelumbo Nucifera Flower Extract	**182**

Strategy Memo - Yeast

In February 2022, data were received suggesting the use of various genus and species of yeasts in the preparation of Yeast Extract, other than Saccharomyces cerevisiae. Because of this, and the broad and uninformative definition of Yeast in the Dictionary, CIR requested the guidance of the Panel in the handling of this report, and the ingredients therein. The Panel suggested the preparation of another strategy memo, to be reviewed at a future meeting, including all yeast ingredients currently listed in the Dictionary, along with notations of whether or not these ingredients (or their corresponding species) are used in foods, and their frequency of use. The Panel also requested the guidance of an expert with knowledge regarding the classification and general biology of yeasts. In addition, information is requested from industry verifying which species of yeast are used in the manufacturing of Yeast and Yeast Extract.

Airbrush Discussion

The Panel expressed concerns on validation of information sources that identify cosmetic formulas associated with airbrush delivery, in consideration of Women's Voices for the Earth (WVE)'s memo, which presented the usage of Kaolin and Acrylates/Octylacrylamide Copolymer in airbrush products. The Panel re-emphasized that data identification process requires transparency and consistency; therefore, data included in CIR reports should come from sources that can be easily validated and verified (e.g., frequency and concentration of use data are crucial in justifying exposure patterns and duration of discrete ingredient use contained in a specific formula) and need to be cited in a way that meets CIR report format requirements.

In addition, the Panel discussed the jurisdictions between different federal agencies regarding the categorization and safety management of consumer products applied with airbrush technologies. The Panel further discussed its purview in a safety evaluation process that requires addressing hazards involving both airbrush device use and exposure of discrete ingredients through sprayable applications, based upon responses recently received from US Consumer Product Safety Commission (CPSC), US FDA Center for Devices and Radiological Health, as well as the Office of Cosmetics and Colors. The Panel re-stated that the data are currently insufficient to assess the inhalation safety of each ingredient in relation to the unintended exposure resulting from the intended use of the finished products delivered by airbrush system.

The Panel determined the following boilerplate language should be included under the Cosmetic Use section of each report that is about to be reviewed at upcoming Panel meetings:

> The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. The cosmetic product categories named in the VCRP database, indicate the intended uses of a cosmetic ingredient, and are identified in 21 CFR Part 720. Data are submitted by the cosmetic industry in response to a survey conducted by the Personal Care Products Council (Council), of maximum reported use concentrations, also by product categories. Neither the categories provided by the VCRP nor those provided by the Council survey, include a designation for use via airbrush application. Airbrush devices, alone, are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients as used in airbrush devices are within the jurisdiction of the FDA. As airbrush technology use for cosmetics has neither been evaluated by the CPSC, nor the use of cosmetic ingredients in airbrush technology by the FDA, no US regulatory authority has evaluated the safety of this delivery methodology for cosmetic ingredients. Moreover, no consumer habits and practices data are available to evaluate the risks associated with this use type.

In addition, when discussing potential safety concerns raised by specific routes of exposure (such as incidental ingestion, eye area, inhalation, etc.), the following paragraph is to be included in reports:

> Additionally, although products containing some of these ingredients may be marketed for use with airbrush technology, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data related to this use technology), the data are insufficient to evaluate the safety thereof in airbrush applications.

The Panel further determined the following statement should go into the Discussion section when the Panel is informed through alternative sources other than the FDA VCRP or the Council survey:

> The Panel acknowledges that some cosmetic ingredients may be used in products marketed for airbrush application. However, the available data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled when applied using airbrush devices. The Panel's respiratory exposure resource document (available here: https://www.cir-safety.org/cir-findings) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. Thus, the data do not support the safety of the ingredients named in this report if applied via airbrush technology.