Post Meeting Announcement

Expert Panel for Cosmetic Ingredient Safety
154th Meeting (June 8-9, 2020) - Findings

June 12, 2020

● Final Safety Assessments

- **Palm (açai and juçara) – 8 ingredients – Safe**
- **Vanilla – 9 ingredient – Split conclusion (safe with qualifications; insufficient for various endpoints)**
- **Pomegranate – 18 ingredients – Split conclusion (safe; insufficient for various endpoints)**
- **Soy – 28 ingredients – Split conclusion (safe; insufficient for various endpoints)**
- **Honey – 7 ingredients – Safe**

● Tentative Safety Assessments

- **Adenosine – 5 ingredients – Safe**
- **MI – 1 ingredient – Safe with qualifications**
- **Wheat – 27 ingredients – Insufficient for various endpoints**
- **Glycerin Ethoxylates – 8 ingredients – Insufficient for sensitization**
- **Methicones – 30 ingredients – Safe with qualifications**
- ***Scutellaria baicalensis* – 4 ingredients – Split conclusion (safe; insufficient for various endpoints)**
- **Ascorbyl Glucoside – 2 ingredients - Safe**
- **Caprylhydroxamic Acid – 1 ingredient - Safe**

● Insufficient Data Announcements

- **Papaya – 5 ingredients**
- **Basic Brown 17 – 1 ingredient**
- **Tris(Tetramethylhydroxypiperidinol) Citrate – 1 ingredient**

● Re-Review

- **Quaternium-18 – closed – prior conclusion affirmed**
- **Sulfites – closed – prior conclusion affirmed**

● 154th Meeting Notes

- **Director's Report**
- **Draft 2021 Priorities**
- **Scientific Literature Reviews – available or under development**
- **Next Expert Panel Meeting – Monday and Tuesday, September 14-15, 2020**

Final Safety Assessments

Final safety assessments will be posted on the CIR website at www.cir-safety.org. Unpublished data cited as references in CIR safety assessments are available for review. Any interested person who has sound scientific evidence that a final safety assessment is incorrect may petition the Expert Panel for Cosmetic Ingredient Safety (Panel) to amend the safety assessment.

Palm (açai and juçara)-Derived Ingredients

The Expert Panel for Cosmetic Ingredient Safety (Panel) concluded that the following 8 palm tree (*Euterpe edulis* (juçara) and *Euterpe oleracea* (açaí)-derived) ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, and issued a final report.

Euterpe Edulis Fruit Extract*	Euterpe Oleracea Juice	Euterpe Oleracea Seed Powder*
Euterpe Edulis Juice Extract*	Euterpe Oleracea Palm Heart Extract	Hydrolyzed Euterpe Oleracea Fruit
Euterpe Oleracea Fruit Extract	Euterpe Oleracea Pulp Powder	

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

The Panel's conclusion on these ingredients was made by taking into consideration the available toxicity data and similarities in composition. Although there was an absence of compositions data for Hydrolyzed Euterpe Oleracea Fruit, the Panel determined that the available composition data on Euterpe Oleracea Fruit Extract and *Euterpe oleracea* fruit were comparable.

It should be noted that, at the December 2019 Panel meeting, the Panel concluded that the available data were insufficient to make a determination that Euterpe Oleracea Palm Heart Extract was safe under the intended conditions of use in cosmetic formulations. The data needs were as follows:

- Composition data
  - If the composition of this ingredient is found to be significantly different from the other ingredients in this group, skin irritation and sensitization data would be needed

The Panel subsequently determined that the need for these data is mitigated, after making the following observations: Palm heart ("hearts of palm") is edible and a commonly consumed part of the palm tree, and there is a lack of consumption-related adverse event reports, such as contact sensitization or colitis, in both the published literature and clinical experience. Additionally, the available data indicate that cosmetic use concentrations of Euterpe Oleracea Palm Heart Extract are rather low, i.e., up to 0.001% in both rinse-off and leave-on products. Therefore, the Panel concluded that Euterpe Oleracea Palm Heart Extract is also safe in the present practices of use and concentration.

Vanilla-Derived Ingredients

The Panel issued a final report with the conclusion that the following 7 vanilla-derived ingredients are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Vanilla Planifolia Fruit Extract	Vanilla Planifolia Seed*	Vanilla Tahitensis Seed*
Vanilla Planifolia Fruit Oil	Vanilla Planifolia Seed Powder	
Vanilla Planifolia Fruit Water	Vanilla Tahitensis Fruit 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.*

While the available human skin sensitization data on Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract are negative, final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern. Thus, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

Concern was mitigated for the positive (++) photo-patch test reactions to vanilla extract which were observed in a photodermatitis patient, because the strength of the reaction at photo-irradiated and non-irradiated sites was the same. Therefore, it was agreed that the observed test results were not due to a photosensitization reaction.

However, the Panel also concluded that the available data are insufficient to make a determination that the following 2 ingredients are safe under the intended conditions of use in cosmetic formulations:

Vanilla Planifolia Flower Extract	Vanilla Planifolia Leaf Cell Extract

The data needed to determine the safety of these 2 ingredients comprise:

- Method of manufacture and impurities
- Composition
- Concentration of use
- 28-day dermal toxicity
  - Depending on the results, other toxicological endpoints may be needed (e.g., genotoxicity and DART)

***Punica granatum* (Pomegranate)-Derived Ingredients**

The Panel issued a final report with the conclusion that the following 9 ingredients are safe in the present practices of use and concentration described in the safety assessment.

Punica Granatum Flower Extract	Punica Granatum Fruit Water	Punica Granatum Seed
Punica Granatum Fruit Extract	Punica Granatum Juice Extract	Punica Granatum Seed Extract
Punica Granatum Fruit Juice	Punica Granatum Pericarp Extract	Punica Granatum Seed Powder

The Panel noted data that indicate that extracts of parts of *Punica granatum* may have a skin lightening effect. Skin lightening is considered to be a drug effect and should not occur during the use of cosmetic products. Based on the concentration of use of these extracts in cosmetic products, the known mechanism of action, the results of an *in vitro* study, and clinical experience, the Panel was not concerned that these ingredients would have these effects in cosmetic products, as they are reported to be used in this safety assessment.

The Panel also concluded that the data were insufficient to support a determination of safety for the following 9 ingredients:

Punica Granatum Extract‡	Punica Granatum Callus Culture Extract*	Punica Granatum Leaf Cell Extract*
Punica Granatum Bark Extract	Punica Granatum Fruit/Root/Stem Powder*	Punica Granatum Peel Extract*
Punica Granatum Bark/Fruit Extract*	Punica Granatum Fruit/Sucrose Ferment Filtrate*	Punica Granatum Seed Cell Culture Lysate*

‡ Ingredient has been deleted from the Dictionary, but uses are currently reported to the FDA Voluntary Cosmetic Registration Program (VCRP).
** Uses not reported.*

The additional data needed for these cosmetic ingredients are:

- Method of manufacturing with regard to solvent-type used for the extracts
- Composition and impurities data
- Systemic toxicity data
- Dermal irritation and sensitization data.

Soy-Derived Ingredients

The Panel issued a final report with the conclusion that 24 of the 28 soy-derived ingredients are safe in the present practices of use and concentration described in the safety assessment.

Glycine Max (Soybean) Fiber*	Glycine Max (Soybean) Seedcoat Extract*	Glycine Soja (Soybean) Lipids
Glycine Max (Soybean) Flower/Leaf/Stem Juice*	Glycine Max (Soybean) Seed Powder*	Glycine Soja (Soybean) Phytoplacenta Extract*
Glycine Max (Soybean) Leaf Cell Extract*	Glycine Max (Soybean) Sprout Extract	Glycine Soja (Soybean) Seed
Glycine Max (Soybean) Leaf Extract*	Glycine Soja (Soybean) Extract	Glycine Soja (Soybean) Seedcake Extract*
Glycine Max (Soybean) Phytoplacenta Extract	Glycine Soja (Soybean) Fiber*	Glycine Soja (Soybean) Seed Extract
Glycine Max (Soybean) Pulp*	Glycine Soja (Soybean) Flour	Glycine Soja (Soybean) Seed Powder*
Glycine Max (Soybean) Seed Extract	Glycine Soja (Soybean) Germ Extract	Glycine Soja (Soybean) Seed Water*
Glycine Max (Soybean) Seedcake Extract*	Glycine Soja (Soybean) Hull*	Glycine Soja (Soybean) 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 determined that there would be no concern for systemic toxicity, as these ingredients have historical food use, and, exposure via oral ingestion would be much higher than exposure from cosmetics. In addition, the Panel considered the reproductive effects following oral ingestion of soybean and soybean extract; however, the effects were likely attributed to the isoflavone and phytoestrogen content. Concern for these reproductive effects was mitigated considering the total isoflavone and phytoestrogen content would be relatively low in cosmetics, and dermal exposure to these ingredients would be far lower than oral exposure.

However, the Panel determined there were insufficient data to determine the safety of the remaining 4 ingredients.

Glycine Max (Soybean) Callus Culture*	Glycine Max (Soybean) Callus Extract*
Glycine Max (Soybean) Callus Culture Extract*	Glycine Max (Soybean) Phytoplacenta Conditioned Media*

The insufficiencies include a lack of:

- Composition
- Impurities
- Method of manufacture
- 28-day dermal toxicity
- Sensitization/irritation data

Honey-Derived Ingredients

The Panel issued a final report with the conclusion that Honey, Honey Cocoates, Honey Powder, Honey Extract, Hydrogenated Honey, Hydrolyzed Honey, and Hydrolyzed Honey Protein are safe in the present practices of use and concentration as described in the safety assessment. The safety of these ingredients is supported by negative sensitization data, historical food use, and use in wound dressings, without adverse effects.

Tentative Safety Assessments

*For those tentative safety assessments below to be posted on the CIR website at www.cir-safety.org on or before **June 19, 2020**, interested persons are given 60 days from the posting date (**August 18, 2020**) to comment, provide information, and/or request an oral hearing before the Expert Panel for Cosmetic Ingredient Safety. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, and are available for review by any interested party. Please submit data and/or comments to CIR **as soon as possible, but no later than August 18, 2020 for full consideration. Submissions received thereafter may be in jeopardy of not being considered by the Panel.** The updated reports may be scheduled for review by the Expert Panel as early as at its **September 14-15, 2020** meeting. However, some of the tentative safety assessments below may be posted later (with an appropriate 60-day comment period) and likely be scheduled for review by the Panel at its **December 7-8, 2020** meeting.*

Adenosine Ingredients

The Panel issued a tentative report for public comment with the conclusion that Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate are safe in the present practices of use and concentration described in the safety assessment. The safety of this ingredient group is supported by sufficient impurities data, negative animal oral toxicity assays, negative human dermal irritation/sensitization assays, and low concentrations of use.

According to data received in 2020 from the FDA VCRP, Adenosine, Adenosine Phosphate, Adenosine Triphosphate, and Disodium Adenosine Triphosphate are reported to be used in 905, 96, 42, and 116 formulations, respectively. The results of a concentration of use survey conducted by the Personal Care Products Council (Council) indicate that Adenosine has the highest concentration of use; it is used at up to 1% in body and hand products.

Methylisothiazolinone (MI)

The Panel issued a tentative amended report with the conclusion that MI is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when formulated to be non-sensitizing, which may be determined based on a quantitative risk assessment (QRA) or similar methodology.

The Panel's recommendations for MI in rinse-off and leave-on cosmetic products are intended to prevent the induction of sensitization to MI. The Panel cautioned that following these recommendations may not necessarily prevent the elicitation of allergic reactions in individuals who are already allergic to MI. Individuals sensitized to MI should avoid products that contain MI.

In response to concerns of reports of adverse events observed in infants following inhalation exposure to humidifier disinfectants that contained the preservative mixture Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI), the Panel moved to reopen the safety assessment of MI in September 2019. A search for inhalation toxicity data regarding MI (separate from the combination of MCI/MI) did not yield any new published literature, aside from the papers already detailed in the MCI/MI report. The Panel reviewed these data as well as the findings of a draft risk assessment for MCI/MI, and a hazard characterization of isothiazolinones produced by the US Environmental Protection Agency, and determined that these data mitigated concern for the use of this ingredient at the reported use and concentrations in cosmetic products that could be incidentally inhaled following use.

Wheat-Derived Ingredients

The Panel issued a tentative report with the conclusion that the data are insufficient to support a determination of safety for the following 27 ingredients:

Triticum Aestivum (Wheat) Flour Lipids
Triticum Aestivum (Wheat) Germ Extract
Triticum Aestivum (Wheat) Leaf Extract
Triticum Aestivum (Wheat) Peptide
Triticum Aestivum (Wheat) Seed Extract
Triticum Monococcum (Wheat) Seed Extract
Triticum Monococcum (Wheat) Stem Water
Triticum Spelta Seed Water
Triticum Turgidum Durum (Wheat) Seed Extract
Triticum Vulgare/Aestivum (Wheat) Grain Extract
Triticum Vulgare (Wheat) Bran
Triticum Vulgare (Wheat) Bran Extract
Triticum Vulgare (Wheat) Bran Lipids
Triticum Vulgare (Wheat) Flour Extract
Triticum Vulgare (Wheat) Flour Lipids
Triticum Vulgare (Wheat) Germ
Triticum Vulgare (Wheat) Germ Extract
Triticum Vulgare (Wheat) Germ Powder
Triticum Vulgare (Wheat) Germ Protein
Triticum Vulgare (Wheat) Gluten
Triticum Vulgare (Wheat) Gluten Extract
Triticum Vulgare (Wheat) Kernel Flour
Triticum Vulgare (Wheat) Protein
Triticum Vulgare (Wheat) Seed Extract
Triticum Vulgare (Wheat) Sprout Extract
Triticum Vulgare (Wheat) Straw Water
Wheat Germ Glycerides

The additional data needed for these cosmetic ingredients are:

- Method of manufacturing data
- Dermal irritation and sensitization data at or above 13% for Triticum Vulgare (Wheat) Sprout Extract.

Glycerin Ethoxylates

The Panel issued a tentative report with the conclusion that the data are insufficient to support a determination of safety for the following 8 glycerin ethoxylate ingredients:

Glycereth-3	Glycereth-8	Glycereth-18	Glycereth-26
Glycereth-7	Glycereth-12	Glycereth-20	Glycereth-31

Previously submitted summary HRIPT data, with test materials 2% Glycereth-7 and 3% Glycereth-26, did not elucidate whether low-level reactions reported during induction and/or challenge occurred repeatedly in the same, or different, participants. Consequently, the Panel issued a second insufficient data announcement (IDA), at the December 2019 meeting, for participant-level, experimental data for these HRIPTs, or, new, complete, experimental data with $n \geq 100$ participants. The Panel was especially interested in receiving complete experimental data for an HRIPT done with the maximum reported concentration of use for the ingredient with the highest reported use, namely, 6% Glycereth-26.

In response to the second IDA, the Panel received details for 2 previously submitted 0.35% and 5% Glycereth-26 HRIPT summaries, and a new HRIPT study, with individual-level data for 10% Glycereth-26, in 200 participants, in which there were no positive reactions. However, the Panel concluded that the quality of the existing data still do not fully support the dermal sensitization safety of these ingredients. Hence, the Panel issued a tentative report with an insufficient conclusion for dermal sensitization.

Methicones

The Panel issued a tentative amended report for public comment with the conclusion that these 30 ingredients are safe when formulated to be non-irritating to the skin and eye.

Stearoxy Dimethicone
Dimethicone
Methicone
Amino Bispropyl Dimethicone
Aminopropyl Dimethicone
Amodimethicone
Amodimethicone Hydroxystearate
Behenoxy Dimethicone
C24-28 Alkyl Methicone
C30-45 Alkyl Methicone
C30-45 Alkyl Dimethicone
Cetearyl Methicone
Cetyl Dimethicone
Dimethoxysilyl Ethylenediaminopropyl Dimethicone

Hexyl Methicone	C20-24 Alkyl Dimethicone*
Hydroxypropyldimethicone	C24-28 Alkyl Dimethicone*
Stearamidopropyl Dimethicone	C26-C28 Alkyl Dimethicone*
Stearyl Dimethicone	C30-60 Alkyl Dimethicone*
Stearyl Methicone	C32 Alkyl Dimethicone*
Vinyl Dimethicone	Caprylyl Methicone*
Capryl Dimethicone*	C20-24 Alkyl Methicone*
Hexyl Dimethicone*	C26-28 Alkyl Methicone*

The Panel first published a review of 20 of these ingredients in 2003, wherein due to large molecular weights and low concentrations of use, this ingredient family was deemed safe as used in cosmetics. In accordance with CIR Procedures, the Panel re-considered these ingredients after 15 years, at the December 2019 meeting. Updated data revealed a dramatic increase in current frequency and concentrations of use, especially in products that might be inhaled, contributing to potential inhalation toxicity concerns. The Panel, therefore, determined to re-open this safety assessment. The CIR Science & Support Committee (SSC) proposed the addition of Simethicone and 10 additional alkyl dimethicone and methicone ingredients (marked with a "*" above). The Panel decided to exclude Simethicone from this review, due to the additional data needs for chemical identity and inhalation toxicity potential of the silica used in cosmetic Simethicone. The Panel's above conclusion on these 30 ingredients is based, in part, upon data suggesting possible ocular irritation resulting from incidental exposure to products used near the eye, especially those containing Dimethicone at concentrations comparable to the maximum reported concentration of use for this category, 37.8%.

***Scutellaria baicalensis*-Derived Ingredients**

The Panel concluded that the following 2 *Scutellaria baicalensis*-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Scutellaria Baicalensis Root Extract Scutellaria Baicalensis Root Powder*

** Not reported to be in current use. Were this ingredient 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 the root extract.*

However, the Panel also concluded that the available data are insufficient to make a determination that the following 2 ingredients are safe under the intended conditions of use in cosmetic formulations:

Scutellaria Baicalensis Extract Scutellaria Baicalensis Sprout Extract

The data needed to determine the safety of these 2 ingredients comprise:

- Genotoxicity (*in vitro* and mammalian); methanol and aqueous extracts should be tested
- Phototoxicity
- Skin irritation and sensitization
- For Scutellaria Baicalensis Extract
  - 28-day dermal toxicity; if dermal absorption occurs, additional data may be needed
- For Scutellaria Baicalensis Sprout Extract
  - Method of Manufacture
  - Composition
  - Impurities
  - Dermal absorption; if dermal absorption occurs, additional data may be needed

In *in vitro* experiments involving B16F10 mouse melanoma cell cultures, *Scutellaria baicalensis* root extracts (both the ethanol extract and methanol extract) had an inhibitory effect on melanogenesis. However, in other experiments involving *Scutellaria baicalensis* root extracts obtained using other extractants (n-hexane, ethyl acetate, and water), an inhibitory effect on melanogenesis in B16F10 mouse melanoma cells was not observed. Given these findings, the Panel noted that if an effect on melanogenesis is observed in a cell culture system only, then a no-effect-level from an *in vivo* experiment would be needed to determine whether or not Scutellaria Baicalensis Root Extract has any effect on melanogenesis. The Panel also noted that skin lightening is considered to be a drug effect, and should not occur during the use of cosmetic products. Because of that caveat and based on the low concentrations of use of Scutellaria Baicalensis Root Extract in cosmetic products, the results of these *in vitro* experiments on *Scutellaria baicalensis* root extracts, and clinical experience of the Panel members, concern for this effect in cosmetics was mitigated.

Ascorbyl Glucoside and Sodium Ascorbyl Glucoside

The Panel concluded that the following ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment and issued a tentative report.

Ascorbyl Glucoside Sodium Ascorbyl Glucoside*

** Not reported to be in current use. Were this ingredient 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 Ascorbyl Glucoside.*

The Panel noted the absence of developmental and reproductive toxicity data on Ascorbyl Glucoside and Sodium Ascorbyl Glucoside. However, concern over the lack of these data were mitigated considering that Ascorbyl Glucoside is metabolized to ascorbic acid and glucose in the skin and would not be absorbed in an appreciable quantity.

The Panel also noted the potential for skin lightening effects and that skin lightening is considered to be a drug effect, and should not occur during the use of cosmetic products. Furthermore, based on the low current use concentrations in cosmetic products, the results of an *in vitro* experiment, and clinical experience, concern for this effect in cosmetics was mitigated.

Caprylhydroxamic Acid

The Panel issued a tentative report for public comment with the conclusion that Caprylhydroxamic Acid is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel was concerned about inconsistent outcomes regarding dermal sensitization. However, upon further review, the Panel determined that studies that had positive sensitization results were those in which the test substance included a penetration enhancer. Additionally,

the Panel noted that cases of increased sensitization with use of a moisturizer in Finland, that had been reformulated to include Caprylhydroxamic Acid, appeared to be related to use on damaged skin, which most likely resulted in increased penetration. Therefore, the Panel stated that caution should be taken with use of Caprylhydroxamic Acid in a manner that would result in increased penetration, such as formulation with penetration enhancers. This is especially important in product types with a margin of safety (MOS), based on an acceptable exposure level/consumer exposure level ratio (AEL/CEL) at or near 1, as calculated in a QRA. According to the results of a QRA 2.0 that was submitted to CIR, product types with an AEL/CEL of 1 include baby lotions, oils, and creams.

Insufficient Data Announcements

For these insufficient data announcements, interested persons are given an opportunity to comment, provide information and/or request an oral hearing before the Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, and are available for review by any interested party. Please submit data and/or comments to CIR ***as soon as possible, but no later than August 11, 2020, for full consideration. Submissions received thereafter might not be considered by the Panel at their next meeting.*** *These reports may be scheduled for review by the Panel as soon as the* ***September 14-15, 2020*** *meeting.*

Papaya-Derived Ingredients

The Panel issued an insufficient data announcement for the following *Carica papaya* (Papaya) derived ingredients:

Carica Papaya (Papaya) Fruit	Carica Papaya (Papaya) Fruit Juice	Carica Papaya (Papaya) Leaf Extract.
Carica Papaya (Papaya) Fruit Extract	Carica Papaya (Papaya) Fruit Water	

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

- For Carica Papaya (Papaya) Fruit Extract
  - Irritation and sensitization on at the reported maximum use concentration of 0.25%
    - Such data might be applicable as a read-across source for the other *Carica papaya* fruit ingredients
- For Carica Papaya (Papaya) Leaf Extract
  - Impurities
  - Genotoxicity
  - Irritation/sensitization

Basic Brown 17

The Panel issued an IDA for the hair dye ingredient, Basic Brown 17. The additional data needs for this ingredient are:

- Concentration of use and reported function for the non-coloring hair product uses that were reported in the FDA VCRP database.

Tris(Tetramethylhydroxypiperidinol) Citrate

The Panel issued an IDA for the ingredient Tris(Tetramethylhydroxypiperidinol) Citrate. The additional data need for this ingredient are:

- Method of manufacture
- Impurities

The Council proposed the addition of available data related to the cosmetic ingredient, Hydroxy Tetramethylpiperidine Oxide, and the non-ingredient, 2,2,6,6-tetramethyl-4-piperidine-*N*-oxide, as read-across sources. The Panel noted the analogous structural features and radical scavenging activity of Tris(Tetramethylhydroxypiperidinol) Citrate, Hydroxy Tetramethylpiperidine Oxide, and 2,2,6,6-tetramethyl-4-piperidine-*N*-oxide, and agreed to these additions.

Re-Reviews

Quaternium-18 and Quaternium-18 Bentonite

The Panel concluded that the reopened safety assessment on Quaternium-18 and Quaternium-18 Bentonite should not advance within the CIR review process, and that a re-review summary should be developed, confirming their prior conclusion. The Panel first reviewed the safety of Quaternium-18 and Quaternium-18 Bentonite in 1982 and concluded that these ingredients are safe as used. In 2001, after considering new studies and updated use data on these ingredients, the Panel confirmed the original conclusion. Because it was at least 15 years since the last review, the Panel re-reviewed Quaternium-18 and Quaternium-18 Bentonite at the September 2019 meeting, and determined to re-open the safety assessment to evaluate the sufficiency of inhalation data on Quaternium-18 Bentonite.

After evaluating the new data and original reports, at the June 2020 meeting, the Panel reaffirmed the original conclusion of safe as used for Quaternium-18 and Quaternium-18 Bentonite. The Panel felt the acute inhalation toxicity study was sufficient to support the use of Quaternium-18 Bentonite in cosmetics, as no toxic effects were observed when animals were exposed to a high concentration of the test substance for a prolonged period of time. In cosmetics, exposure to Quaternium-18 Bentonite in potentially inhaled products would be brief and at low concentration. In addition, the concentrations and number of uses for both Quaternium-18 and Quaternium-18 Bentonite have decreased since 2001. Quaternium-18 Bentonite was previously reported to be used at up to 9% in leave-on products, however, according to 2018 concentration of use data, Quaternium-18 Bentonite is reported to be used at up to 2.5% in leave-on products. The Panel considered the concern for developmental/reproductive toxicity or genotoxicity mitigated by the lack of dermal penetration, chronic oral toxicity, and dermal toxicity.

Sulfites

The Panel concluded that the reopened safety assessment on the following 7 sulfites should not advance within the CIR review process, and that a re-review summary should be developed, confirming their prior conclusion.

Ammonium Bisulfite	Potassium Metabisulfite	Sodium Bisulfite	Sodium Sulfite
Ammonium Sulfite*	Potassium Sulfite	Sodium Metabisulfite	

** Not reported to be in current use. Were this ingredient 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 first reviewed the safety of Sulfites in 2003. The Panel concluded that Ammonium Bisulfite, Ammonium Sulfite, Potassium Metabisulfite, Potassium Sulfite, Sodium Bisulfite, Sodium Metabisulfite, and Sodium Sulfite are safe as used in cosmetic formulations. Because it has been at least 15 years since this report was published, in accordance with CIR Procedures, the Panel considered new studies and updated use data on these ingredients at the September 2019 Panel meeting. Furthermore, the Panel considered the increased ingredient use frequency, reports of dermal sensitization, enhanced asthmatic responses to dust mites, and mutagenic effects in the published literature.

The Panel's concern about sulfite-induced dermal sensitization, following a review of patient studies, was allayed after considering negative results from two HRIPTs on Sodium Sulfite at concentrations greater than 0.25% (the highest reported concentration in leave-on products) in healthy subjects. The Panel noted that results from a patient population are difficult to interpret in terms of their relevance to the general population, and, also, that reactions to sulfites on standard panels used by dermatologists are rare. However, the Panel acknowledged that sulfites may cause hypersensitivity, as evidenced by the enhancement of allergic sensitization (i.e., IgE-mediated allergy) in dust mite allergen-sensitized BALB/c mice. Additionally, the Panel noted that sulfites are associated with IgE-mediated allergic reactions in some individuals, and that individuals with sulfite allergies should exercise caution in using products containing sulfites that may be incidentally inhaled.

After considering that positive genotoxicity results (sister chromatid exchanges) were observed at the highest dose tested, the Panel agreed that such a high dose would not be achieved during cosmetic product use. Furthermore, the Panel noted that the weight of evidence for sulfite-induced carcinogenicity in animal models is negative, and that the International Agency for Research on Cancer has concluded that there is inadequate evidence for the carcinogenicity of sulfites in experimental animals and humans. The mitigation of concern by the Panel over the potential toxicity of sulfites from cosmetic exposure is also based on the use of these ingredients at low concentrations and the low potential for absorption.

154th Meeting Notes

Director's Report

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the Cosmetic Ingredient Review program. He also reported on a number of firsts for the Panel. Prominently, this was the first ever virtual meeting for the Panel, and it was a complete success.

Secondly, the name of the Panel is henceforth changed from the CIR Expert Panel to the Expert Panel for Cosmetic Ingredient Safety. Much like members of an FDA Advisory Committee for pharmaceutical assessments are not employees of FDA, members of the Panel are not employees of CIR. This change in name was intended to be a first step in clarifying that distinction. Further to that end, a new website has been created exclusively for the Panel: ingredientsafetyexpertpanel.org. Therein, the mission, composition, and an explanation of the Panel's definition of a conflict of interest, are now publicly available.

Sadly, the September 2020 meeting will be the last meeting with Dr. Marks serving as a member of this Panel, as he is retiring therefrom. Accordingly, Dr. Heldreth is seeking nominations to fill this seat on the Panel. Nominees should be experts in dermatology and have no conflicts of interest as defined at ingredientsafetyexpertpanel.org/conflict-of-interest-statement. Nominations may be submitted to cirinfo@cir-safety.org, no later than June 26, 2020.

Draft 2021 Priorities

The priority list is typically based on stakeholder requests ("for cause," 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 13 (in response to a Freedom of Information Act request).

While this list includes only the lead ingredients, groupings of botanical, or other organism-sourced mixture-type, ingredients (e.g., Rosa Centifolia Flower Extract), were drafted in the meeting materials for potential inference groupings, based on species and plant part(s). However, for organic chemicals, the list of lead ingredients was forwarded to the newly convened CIR Grouping/Clustering Working Group for consideration. The Working Group's input will be incorporated into the Draft Final 2021 Priorities, to be presented at the September 2020 meeting.

There are 11 reports proposed (2 of the lead ingredients below are proposed to be reviewed together in 1 report) on the 2021 Draft Priorities List. Reports previously prioritized and on the CIR docket at the end of 2020, as well as a number of re-reviews of previous assessments, will supplement the total number of reports to be assessed in 2021.

Ingredients	Frequency of Use (FOU) Data Year 2020
For cause	
Basic Yellow 57 – a hair dye	45
Per FOU	
Yeast Extract	736
Glyceryl Acrylate/Acrylic Acid Copolymer	519
Hydroxyacetophenone	409
Glyceryl Polymethacrylate	364
Acrylates/Octylacrylamide Copolymer	361
Hydroxypropyl Starch Phosphate	353
Sodium Lauroamphoacetate	344
Zingiber Officinale (Ginger) Root Extract	326
Leuconostoc/Radish Root Ferment Filtrate	322
Rosa Centifolia Flower Extract	321
Phytosteryl/Octyldodecyl Lauroyl Glutamate	313

Interested parties are encouraged to submit pertinent data to the CIR, as soon as possible, for use in the development of the Scientific Literature Reviews for these ingredients. Although the specific data needs vary for each safety assessment, the following are typical data that the Panel reviews for each safety assessment.

- Chemistry, impurities, and method of manufacture
- Toxicokinetics data, specifically dermal absorption and/or penetration
- Repeated-dose toxicity data

• Inhalation toxicity data, if the ingredient is used in a product that can be incidentally inhaled

• Reproductive/developmental toxicity data

• Genotoxicity data; if positive, carcinogenicity data may be needed

• Dermal irritation and sensitization data at maximum concentration of use

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

Scientific Literature Reviews

The following Scientific Literature Reviews are posted at the CIR website or are currently under development and may be posted imminently. These may then be presented to the Panel for their review (as Draft Reports) during the next few meetings.

- Acetyl Hexapeptide-8 and Acetyl Hexapeptide-8 Amide
- Acrylate/Acrylamide Copolymers
- Acryloyloxyethyl Phosphorylcholine Polymers
- Diacetone Alcohol
- Diatomaceous Earth
- *Equisetum arvense*-Derived Ingredients
- Glycolactones
- *Hordeum vulgare*-Derived Ingredients
- Levulinic Acid & Sodium Levulinate
- *Melaleuca alternifolia* (Tea Tree)-Derived Ingredients
- Polyquaternium-6
- *Portulaca oleracea*-derived Ingredients
- Red Algae-Derived Ingredients
- *Rosa damascena*-derived Ingredients
- Saccharide Humectants
- *Saccharum officinarum* (sugarcane)- Ingredients
- Ubiquinone Ingredients

Next CIR Expert Panel Meeting

Monday and Tuesday, September 14-15, 2020, to be held virtually via Microsoft Teams.
Please submit a request for an invitation prior to the meeting if you would like to attend. The link will be available approximately a month before the meeting and will be found on the 155th meeting page of the CIR website.