Post Meeting Announcement

Cosmetic Ingredient Review Expert Panel
144th Meeting (September 11-12, 2017) - Findings

September 15, 2017

● Final Safety Assessments

- **Bovine Milk Proteins and Protein Derivatives – 16 ingredients – Safe as used**
- **Plant-Derived Proteins and Peptides – 19 ingredients – Split conclusion**
- **Skin and Connective Tissue-Derived Proteins and Peptides – 19 ingredients – Safe as used**
- ***Butyrospermum parkii* (Shea)-Derived Ingredients – 13 ingredients – Safe with non-sensitizing caveat**
- ***Humulus lupulus* (hops) Extract and Oil – 2 ingredients – Safe with non-sensitizing caveat**
- **Monoalkylglycol Dialkyl Acid Esters – 28 ingredients – Safe as used**
- **Polyurethanes – 66 ingredients – Safe as used**

● Tentative Safety Assessments

- **Triglycerides – 51 ingredients – Safe as used**
- **Alkane Diols – 10 ingredients – Split conclusion**
- **Ammonia and Ammonium Hydroxide – 2 ingredients – Safe with non-irritating caveat**
- **Panthenol, Pantothenic Acid, and Derivatives – 7 ingredients – Safe as used**
- ***Mentha piperita* (Peppermint)-Derived Ingredients – 10 ingredients – Split conclusion**
- **Polyaminopropyl Biguanide – 1 ingredient - Insufficient data**

● Insufficient Data Announcements

- ***Hamamelis virginiana* (Witch Hazel)-Derived Ingredients – 8 ingredients**
- **Alkyl Sultaines – 13 ingredients**

● 144th Meeting Notes

- **Director's Report**
- **Presentations**
- **Other Items**
  - **Precedents (Guidance Documents)**
  - **Re-Review Summaries**
- **Scientific Literature Reviews under development**
- **Next Expert Panel Meeting – Monday and Tuesday, December 4-5, 2017**

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 Unpublished data cited as references in CIR safety assessments are available for review.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 believes that a final safety assessment is incorrect may petition the CIR Expert Panel to amend the safety assessment.

Bovine Milk Proteins and Protein Derivatives

The Cosmetic Ingredient Review Expert Panel (Panel) issued a final report with the conclusion that the 16 bovine milk protein and protein derivative ingredients listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Ammonium Caseinate*	Hydrolyzed Milk Protein	Potassium Caseinate*
Calcium Caseinate*	Hydrolyzed Whey Protein	Sodium Caseinate
Casein	Hydrolyzed Yogurt Protein	Sodium Hydrolyzed Casein*
Casein Extract*	Lactoglobulin	Whey Protein
Hydrolyzed Casein	Milk Protein	
Hydrolyzed Lactalbumin*	Milk Protein 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 Sodium Caseinate has use concentrations reported up to 96.9%; however, this concentration is in bath oils, tablets, and salts, which are diluted in water prior to use. In leave-on products, the maximum concentration of use reported in the casein-derived ingredients is 2%. Safety test data of Hydrolyzed Casein were negative at up to 30%. Because of these factors, the Panel was not concerned with the use of Sodium Caseinate at such a high concentration in diluted bath products.

The Panel noted that bovine milk proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. The Panel reviewed studies showing no relevant ocular irritation and no dermal irritation or sensitization in animals and human subjects. Additionally, according to their collective knowledge in treating patients with Type 1 hypersensitivity, the Panel clinicians have not experienced responses to bovine milk protein via dermal exposures. Thus, the Panel was not concerned that Type I reactions would be induced by dermal exposure to bovine milk proteins in cosmetics.

Plant-Derived Proteins and Peptides

The Panel issued a final report with the conclusion that the following 18 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Hydrolyzed Amaranth Protein	Hydrolyzed Hazelnut Protein	Hydrolyzed Sesame Protein
Hydrolyzed Avocado Protein*	Hydrolyzed Hemp Seed Protein	Hydrolyzed Sweet Almond Protein
Hydrolyzed Barley Protein	Hydrolyzed Jojoba Protein	Hydrolyzed Vegetable Protein
Hydrolyzed Brazil Nut Protein	Hydrolyzed Lupine Protein	Hydrolyzed Zein*
Hydrolyzed Cottonseed Protein	Hydrolyzed Pea Protein	Lupinus Albus Protein
Hydrolyzed Extensin	Hydrolyzed Potato Protein	Pisum Sativum (Pea) Protein

*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 also concluded the data on Hydrolyzed Maple Sycamore Protein are insufficient to determine safety. This ingredient is not reported to be in use.

The following data are needed to evaluate the safety of Hydrolyzed Maple Sycamore Protein:

- Method of manufacturing
- Chemical composition and impurities
- Clarification on food safety status, specifically if this ingredient is generally recognized as safe (GRAS). If this ingredient is not GRAS, then studies of systemic endpoints such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity are needed, as well as UV absorption spectra

The Panel acknowledged that Type I immediate hypersensitivity reactions could possibly occur following exposure to a protein-derived ingredient. Traditional human repeat insult patch tests (HRIPTs) and related tests do not detect Type I reactions. Thus, the Panel recommended that people with known allergies to tree nut, seed, and avocado proteins avoid using personal care products that contain these ingredients.

Skin and Connective Tissue-Derived Proteins and Peptides (previously "Ectodermal-Derived Proteins and Peptides")

The Panel issued a final report with the conclusion that the 19 skin and connective tissue-derived proteins and peptides listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Ammonium Hydrolyzed Collagen
Atelocollagen
Calcium Hydrolyzed Collagen*
Collagen
Elastin
Fibronectin
Gelatin
Hydrolyzed Actin
Hydrolyzed Collagen
Hydrolyzed Collagen Extract*
Hydrolyzed Elastin
Hydrolyzed Fibronectin
Hydrolyzed Gelatin*
Hydrolyzed Reticulin
Hydrolyzed Spongin*
MEA-Hydrolyzed Collagen
Soluble Collagen
Soluble Elastin*
Zinc Hydrolyzed Collagen*

*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 there was a lack of systemic toxicity data (i.e. reproductive and developmental toxicity, genotoxicity, and carcinogenicity data); however, the Panel was not concerned that these proteins and peptides would cause adverse systemic effects in the general population. These proteins and peptides, similar to the other proteins and peptides reviewed by the Panel, are found in food, and daily exposures from the consumption of foods can be expected to yield much larger systemic exposures to these ingredients than those from use in cosmetic products. The Panel also found that the earlier assessments of Hydrolyzed Collagen supported the safety of these ingredients in cosmetic products.

The Panel noted that fish proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. The Panel expressed concern that sensitized individuals would not easily recognize cosmetic products containing fish-derived collagen based on the current naming conventions used in the ingredient lists on product labels (e.g., Collagen and Hydrolyzed Collagen may be sourced from fish, though "fish" is not in the ingredient name). In the absence of negative Type I immediate hypersensitization data for fish-derived protein ingredients (or other information supporting an inability of the supplied ingredient to elicit such sensitization (e.g., a maximum peptide length that is shorter than the minimum IgE-binding epitopes)), the Panel advised manufactures to label products containing these fish-derived ingredients as appropriate to inform individuals sensitized to fish proteins.

***Butyrospermum parkii* (Shea)-Derived Ingredients**

The Panel issued a final report with the conclusion that the following 13 ingredients are safe in cosmetics in the present practices of use and concentration as described in the safety assessment when formulated to be non-sensitizing.

Butyrospermum Parkii (Shea) Butter
Butyrospermum Parkii (Shea) Oil
Butyrospermum Parkii (Shea) Butter Extract
Butyrospermum Parkii (Shea) Butter Unsaponifiables
Butyrospermum Parkii (Shea) Nut Extract
Butyrospermum Parkii (Shea) Nut Shell Powder
Butyrospermum Parkii (Shea) Seedcake Extract
Hydrogenated Shea Butter
Hydrogenated Shea Oil*
Hydrolyzed Shea Seedcake Extract*
Shea Butter Glyceride
Shea Butter Glycerides
Shea Oleine

*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, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one formulation may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels in final formulation of botanical constituents that may cause sensitization or other adverse effects.

There are no irritation or sensitization data for Butyrospermum Parkii (Shea) Nut Extract and Butyrospermum Parkii (Shea) Nut Shell Powder and no irritation or sensitization data for Butyrospermum Parkii (Shea) Seedcake Extract and Butyrospermum Parkii (Shea) Butter at maximum use concentrations (5.5% and 100% in leave-on products, respectively). HRIPTs for Butyrospermum Parkii (Shea) Seedcake Extract and Butyrospermum Parkii (Shea) Butter were negative when tested, although, these were tested at concentrations lower than the maximum use concentrations. However, based on the Panel's clinical experience, the absence of adverse event reports, and the available negative safety test data, the Panel does not expect dermal irritation or sensitization following exposure to these ingredients.

***Humulus lupulus* (Hops) Extract and Oil**

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

Humulus Lupulus (Hops) Extract
Humulus Lupulus (Hops) Oil*

*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 other ingredient in this group.

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one formulation may each contribute to the final concentration of a single shared constituent. Therefore, when formulating products, manufacturers should avoid reaching levels, in final formulations, of botanical constituents that may cause sensitization or other adverse effects.

Humulus Lupulus (Hops) Extract was reported to be used in 375 formulations, including 317 leave-on formulations and 54 rinse-off formulations. The highest reported maximum concentration of use was < 0.2% in hair conditioners; in products intended for dermal contact, the maximum concentration of use is 0.13% in eye lotions, deodorants, and other skin care preparations.

Monoalkylglycol Dialkyl Acid Esters

The Panel issued a final report with the conclusion that the following 28 monoalkylglycol dialkyl acid esters are safe in cosmetics in the present practices of use and concentration as described in the safety assessment.

Butylene Glycol Dicaprylate/Dicaprate
Butylene Glycol Diisononanoate*
Diethylpentanediol Dineopentanoate
Dioctadecanyl Didecyltetradecanoate*
Dioctadecanyl Ditetradecyloctadecanoate*
Glycol Dibehenate*
Glycol Diethylhexanoate
Glycol Dilaurate
Glycol Dioleate*
Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate*
Glycol Dipalmate/Rapeseedate/Soyate*
Glycol Dipivalate*
Glycol Distearate
Glycol Ditallowate*
Hexanediol Distearate*
Neopentyl Glycol Dicaprate
Neopentyl Glycol Dicaprylate/Dicaprate
Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate*
Neopentyl Glycol Diethylhexanoate
Neopentyl Glycol Diheptanoate
Neopentyl Glycol Diisononanoate
Neopentyl Glycol Diisostearate
Neopentyl Glycol Dilaurate*
Propanediol Dicaprylate
Propanediol Dicaprylate/Caprate
Propanediol Diisostearate*
Propanediol Dipelargonate*
Trimethyl Pentanyl Diisobutyrate

*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 acute dermal toxicity tests of the smaller molecules (i.e., Neopentyl Glycol Diisononanoate and Trimethyl Pentanyl Diisobutyrate) revealed no concerns, and acute oral toxicity test results presented little concern. The Panel also considered the safety profile of potential hydrolysis products (e.g., resulting from esterases in the skin) of these ingredients, many of which were determined to be safe in previous CIR safety assessments. A concurrent report, Alkane Diols, also provided safety information about such hydrolysis products (or chemical surrogates thereof), 1,5-Pentanediol and Isopentyldiol, which the Panel considered in the overall weight of evidence. The Panel also noted that their lowered level of concern for the potential hydrolysis products of Diethylpentanediol Dineopentanoate was influenced in part by the maximum concentration of use of this ingredient of only up to 1% in rinse-off products.

Glycol Distearate was reported to be used in 1663 formulations, mostly in hair products (1041 formulations); Trimethyl Pentanyl Diisobutyrate is used in 399 formulations (all nail products), and Neopentyl Glycol Diheptanoate is used in 415 formulations (mostly in skin care products), respectively. The rest of the ingredients with reported uses were used in 102 or fewer formulations. Neopentyl Glycol Diethylhexanoate had the highest reported maximum concentration of use; it is used at up to 57% in leave-on products. Neopentyl Glycol Dicaprate had the next highest reported maximum concentration of use; it is used up to 50% in rinse-off products and 40% in leave-on products.

Polyurethanes

The Panel issued a final report on the following 66 polyurethane ingredients with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration as described in the safety assessment.

Polyurethane-1	Polyurethane-16	Polyurethane-33	Polyurethane-49*	Polyurethane-63*
Polyurethane-2	Polyurethane-17*	Polyurethane-34	Polyurethane-50*	Polyurethane-64*
Polyurethane-4*	Polyurethane-18	Polyurethane-35	Polyurethane-51*	Polyurethane-65*
Polyurethane-5*	Polyurethane-19*	Polyurethane-36*	Polyurethane-52*	Polyurethane-66*
Polyurethane-6	Polyurethane-20*	Polyurethane-39	Polyurethane-53*	Polyurethane-67*
Polyurethane-7	Polyurethane-21*	Polyurethane-40	Polyurethane-54*	Polyurethane-68*
Polyurethane-8	Polyurethane-23*	Polyurethane-41*	Polyurethane-55*	Polyurethane-69*
Polyurethane-9	Polyurethane-24	Polyurethane-42*	Polyurethane-56*	Polyurethane-70*
Polyurethane-10	Polyurethane-25*	Polyurethane-43*	Polyurethane-57*	Polyurethane-71*
Polyurethane-11	Polyurethane-26*	Polyurethane-44*	Polyurethane-58*	Polyurethane-72*
Polyurethane-12*	Polyurethane-27*	Polyurethane-45*	Polyurethane-59*	
Polyurethane-13*	Polyurethane-28*	Polyurethane-46	Polyurethane-60*	
Polyurethane-14	Polyurethane-29*	Polyurethane-47*	Polyurethane-61*	
Polyurethane-15	Polyurethane-32*	Polyurethane-48*	Polyurethane-62*	

* 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 reviewed the method of manufacturing information and the available data on impurities related to these ingredients, and determined that residual monomers would be expected to be either consumed in reaction or washed away in manufacturing and purification processes. Producers and formulators should continue to use good manufacturing principles to prevent conditions wherein monomers could be released from these polymeric ingredients.

Many of these ingredients are reported to be supplied (in pre-formulations or tradename mixtures) as emulsions or solutions with multiple components, sometimes including sensitizers such as methylisothiazolinone (MI; e.g., Polyurethane-60 and -61). Suppliers and formulators (finishing houses) should be

aware of how these polymer ingredients are supplied, and should avoid reaching levels of components that may cause sensitization or other adverse health effects.

Polyurethane-11 was reported to be used in 315 formulations, including 303 leave-on formulations and 12 rinse-off formulations. The other ingredients were reported to have uses in 33 or fewer formulations. Polyurethane-1 has the highest reported maximum concentration of use, at up to 15% in nail products. The highest maximum concentration of use reported for products resulting in leave-on dermal exposure is 7.5% for Polyurethane-33 in the other skin care preparations category. The other reported maximum concentrations of use were at up to 9% (in nail, hair, or rinse-off dermal preparations).

Tentative Safety Assessments

*Tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before **September 22, 2017**. Interested persons are given 60 days to comment, provide information and/or request an oral hearing before the CIR Expert 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.** The updated reports may be scheduled for review by the CIR Expert Panel at its **December 4-5, 2017** meeting.*

Triglycerides

The Panel issued a tentative amended report for public comment with the conclusion that the 51 triglycerides listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Acetic/Linoleic/Palmitic Triglyceride*
C12-18 Acid Triglyceride
C18-36 Acid Triglyceride
C8-12 Acid Triglyceride*
Capric/Lauric/Myristic/Oleic Triglyceride*
Caprylic/Capric Triglyceride
Caprylic/Capric/Lauric Triglyceride
Caprylic/Capric/Linoleic Triglyceride
Caprylic/Capric/Myristic/Stearic Triglyceride
Caprylic/Capric/Palmitic/Stearic Triglyceride*
Caprylic/Capric/Stearic Triglyceride
C10-40 Isoalkyl Acid Triglyceride
Cod Liver/Mink/Tallow Triglyceride*
C10-18 Triglycerides
Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride*
Glyceryl Stearate Diacetate*
Glyceryl Triacetyl Hydroxystearate
Glyceryl Triacetyl Ricinoleate
Glyceryl Tri-Hydrogenated Rosinate
Glyceryl Tripalmate/Palm
Kernelate/Olivate/Macadamiate/Rapeseedate*
Hydrogenated C12-18 Triglycerides
Isomerized Safflower Glycerides*
Jojoba Oil/Caprylic/Capric Triglyceride Esters*
Lauric/Palmitic/Oleic Triglyceride*
Oleic/Linoleic Triglyceride*
Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride*
Palmitic/Stearic Triglyceride
Ricinoleic/Caproic/Caprylic/Capric Triglyceride*
Triarachidin*
Tribehenin
Tricaprin
Tricaprylin
Tierucin*
Triethylhexanoin
Triheptanoin
Triheptylundecanoin*
Trihydroxystearin
Triisononanoin
Triisopalmitin*
Triisostearin
Trilaurin
Trilinolein
Trilinolenin
Trimyristin
Triolein
Tripalmitin
Tripalmitolein*
Tripelargonin*
Triricinolein*
Tristearin
Triundecanoin

*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.

This amended report comprises 25 previously-reviewed ingredients, and 26 ingredients being reviewed for the first time. The Panel agreed that it was appropriate to remove Glyceryl Tribehenate/Isostearate/Eicosandioate from, and to add Tripelargonin to, the list of ingredients included in this report. Glyceryl Tribehenate/Isostearate/Eicosandioate is actually a bis(triglyceride) and, therefore, not appropriate for inclusion in this family. Tripelargonin is a triglyceride that was added to the database of potential cosmetic ingredients (web version of the *International Cosmetic Ingredient Dictionary and Handbook* (wINCI)) after the inception of the safety assessment, and, therefore, it has been added to the report.

An insufficient data announcement (IDA) was issued at the April meeting, requesting irritation and/or sensitization data at maximum concentrations of use for several representative ingredients. Information was received to address some, but not all, of the requests. However, the Panel was confident that the weight of the evidence for safety was very strong, and that the available information was applicable to the entire group.

In the IDA from the April Panel meeting, the Panel also asked for clarification of the skin bleaching potential of Docosahexenoic/Docosapentenoic/Oleic/ Palmitic Triglyceride, including a dose-response for this action. These data were not received. However, the Panel stated that in the U.S., skin bleaching is not considered a cosmetic function, and, therefore, use in that manner is not being assessed in this report.

Finally, the Panel recognized that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals. Accordingly, the Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on a lack of dermal absorption, or wherein dermal absorption was a concern.

Alkane Diols

The Panel issued a revised tentative report for public comment with a split conclusion. The following 6 alkane diols are safe as used in cosmetics in the present practices of use and concentration as described in the safety assessment.

Propanediol	1,10-Decanediol	Butyl Ethyl Propanediol
Hexanediol	Methylpropanediol	Isopentyldiol

However, the Panel determined that the data on the following 4 ingredients are insufficient to determine safety.

1,4-Butanediol	1,5-Pentanediol*	2,3-Butanediol*	Octanediol

*Not reported to be in current use.

The data that are needed to evaluate the safety of 1,4-Butanediol; 1,5-Pentanediol; 2,3-Butanediol; and Octanediol comprise:

- Maximum concentration of use
- Short-term and chronic systemic toxicity data, specifically 28-day dermal toxicity studies
- Mammalian mutagenicity studies

The Panel highlighted the need for concentrations of use for the four ingredients listed above, especially for 1,4-Butanediol, as it can be metabolized into gamma-hydroxybutyric acid (GHB), a controlled substance in the United States. The Panel also expressed concern that the toxicity data that do exist in this report cannot be confidently read across to the other ingredients that lack data. Toxicity data specific to 1,4-Butanediol; 1,5-Pentanediol; 2,3-Butanediol; and Octanediol are necessary to enable the Panel to assess the safety of this full group of ingredients.

The Panel noted that ocular irritation was observed for Butyl Ethyl Propanediol in rabbit studies. The ocular studies for the other alkane diols in this report largely indicated that these ingredients would not be ocular irritants. Given this weight of evidence, and in light of the exposure information that Butyl Ethyl Propanediol is not reported to be used in cosmetics that are used in the eye area, the Panel did not consider the use of the caveat, "formulated to be non-irritating," applicable to this conclusion.

Ammonia and Ammonium Hydroxide

The Panel issued a tentative report for public comment with a conclusion that Ammonia and Ammonium Hydroxide are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

It was noted that Ammonia and Ammonium Hydroxide, well-known skin irritants, are indistinguishable from each other in aqueous formulation. Furthermore, since the only cosmetic function of Ammonia applicable to this safety assessment is pH adjuster (which by default means aqueous formulations only) and Ammonium Hydroxide does not exist outside of water, regardless of which ingredient is added, the final formulations will contain an equilibrium of molecular Ammonia and the ions of Ammonium Hydroxide in water. Thus, whether toxicity data is reported for Ammonia or Ammonium Hydroxide, it is applicable to both (as the test articles would have had this same equilibrium).

The Panel agreed that the cosmetic ingredients Ammonium Chloride and Ammonium Sulfate, which, unlike Ammonia and Ammonium Hydroxide, would not function as pH adjusters in cosmetics, should not be counted in this safety assessment, though they agreed that the data on these other ingredients were useful as surrogates.

Panthenol, Pantothenic Acid, and Derivatives

The Panel issued a tentative report for public comment with the conclusion that the following 7 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Panthenol	Panthenyl Ethyl Ether Acetate*	Sodium Pantothenate*
Pantothenic Acid	Panthenyl Triacetate	
Panthenyl Ethyl Ether	Calcium Pantothenate	

*Not reported to be in current use. Were the ingredients in this group not currently in 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 recognized that these ingredients, particularly Panthenol, can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The Panel also noted that these ingredients may contain residual amines as impurities. The Panel cautioned that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

***Mentha piperita* (Peppermint)-Derived Ingredients**

The Panel issued a tentative report for public comment with a conclusion stating that the available data are insufficient to make a determination of safety for 9 out of the 10 *Mentha piperita* (peppermint)-derived ingredients. These 9 ingredients, and the data that are needed to complete this safety assessment, are stated below.

Mentha Piperita (Peppermint) Leaf Extract
Mentha Piperita (Peppermint) Leaf
Mentha Piperita (Peppermint) Leaf Water
Mentha Piperita (Peppermint) Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water*
Mentha Piperita (Peppermint) Leaf Cell Extract*
Mentha Piperita (Peppermint) Leaf Juice*
Mentha Piperita (Peppermint) Meristem Cell Culture*

*Not reported to be in use.

The data needed to formulate a conclusion of safety include:

- Composition data on each of the above ingredients.
    - Depending on the composition data that are received, other toxicological endpoints may be needed.
- Skin irritation and sensitization data on all of the above ingredients, except Mentha Piperita (Peppermint) Leaf Extract and Mentha Piperita (Peppermint) Leaf Water.

However, it was determined that Mentha Piperita (Peppermint) Oil is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one formulation may each contribute to the final concentration of a single shared constituent. Therefore, when formulating products, manufacturers should avoid reaching levels, in final formulations, of botanical constituents that may cause sensitization or other adverse effects.

This group of ingredients was established at the April 2017 Expert Panel meeting, whereby the Panel agreed that the original final report (published in 2001) on Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water should be reopened to add 6 *Mentha piperita* (peppermint)-derived ingredients. Therein, the Panel also issued an IDA relating to all 10 ingredients, and composition, irritation, and sensitization data were requested.

Data were received in response to the IDA. The Panel agreed that the available composition data on Mentha Piperita (Peppermint) Oil are sufficient, but the data relating to composition of the other ingredients, are inadequate. After considering the available skin irritation and sensitization data, the Panel determined that skin sensitization data on all ingredients, except for the Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita (Peppermint) Leaf Water, are still insufficient.

The Panel considered the positive effects that were observed in female rats, and in male and female mice, dosed with pulegone (component of Mentha Piperita (Peppermint) Oil) in the 2011 National Toxicology Program (NTP) oral carcinogenicity study. However, the Panel did not express concern over these findings relative to pulegone as a component of Mentha Piperita (Peppermint) Oil in cosmetic products, based on the understanding that the cytotoxic dose-response relationship (renal and liver toxicity) that was associated with cancer development would not be relevant to pulegone exposure from a cosmetic product. The Panel also reconsidered the 1% concentration limit on pulegone in the published final report on *Mentha piperita* (peppermint)-derived ingredients that appears to have been based on observations of brain lesions in rats. As the brain lesions were an artifact of the fixation method, the Panel determined that this study was not relevant to cosmetic safety. It was therefore agreed, that the 1% concentration limit and the carcinogenicity of pulegone should be addressed in the report discussion and not in the conclusion.

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

The Panel issued a tentative report with a conclusion stating that the available data are insufficient to make a determination that Polyaminopropyl Biguanide is safe under the intended conditions of use in cosmetic formulations. The data that are needed to complete the safety assessment of this ingredient are:

- HRIPT on Polyaminopropyl Biguanide involving a diverse population (i.e., with a range of Fitzpatrick skin types) of 100 subjects tested with a dose of 1,000 $\mu g/cm^2$ (and recommend to test at 500 $\mu g/cm^2$ as well)
- Consumer use data on pump and propellant hair sprays, for use in estimating the extent of exposure to Polyaminopropyl Biguanide during spray product use

In response to a previous IDA, a spray model and a no observed adverse effect concentration (NOAEC) were used to calculate a margin of safety (MOS). MOS values for both pump hair sprays and propellant hair sprays were calculated. In reviewing this risk assessment, the Panel noted that the exposure scenario (e.g., sprayed over 6 hours) in one of the underlying experimental studies was not representative of pump and propellant hair spray product use. Thereby, consumer use data on these product types are needed to determine a dose, if the safe use of this ingredient is to be determined for products that are intended to be sprayed. However, this ingredient might not actually be in use in products that are intended to be sprayed. Indeed, one supplier submitted a comment that their company would not consider using this ingredient in such applications.

A quantitative risk assessment (QRA) yielded a no expected sensitization induction level (NESIL) of 1000 $\mu g/cm^2$, which theoretically supports the use of this ingredient at concentrations of $\leq 0.1\%$. However, the Panel noted that the HRIPT study utilized to support this NESIL may not be adequately diverse, and suggested that an HRIPT ($\geq$100 subjects) on a more diverse study population at a dose of 500 and 1,000 $\mu g/cm^2$ is needed to derive an acceptable NESIL.

The Panel noted the contact urticaria potential of Polyaminopropyl Biguanide, but determined that this would not be an issue in relation to cosmetic product applications after considering that contact urticaria was observed under the conditions of burn dressings on severely damaged skin. It was also determined that the skin irritation potential of Polyaminopropyl Biguanide at cosmetic use concentrations is not a concern, based on the studies in the assessment.

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 CIR Expert 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****. These reports may be scheduled for review by the CIR Expert Panel at its* ***December 4-5, 2017*** *meeting.*

Hamamelis virginiana **(Witch Hazel)-Derived Ingredients**

The Panel issued an insufficient data announcement for the following 8 *Hamamelis virginiana* (witch hazel)-derived ingredients.

Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract*
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract*
Hamamelis Virginiana (Witch Hazel) Extract
Hamamelis Virginiana (Witch Hazel) Flower Water
Hamamelis Virginiana (Witch Hazel) Leaf Extract
Hamamelis Virginiana (Witch Hazel) Leaf Water
Hamamelis Virginiana (Witch Hazel) Water

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

The data needs are:

- Sensitization data on Hamamelis Virginiana (Witch Hazel) Extract at the highest concentration of use.
- Clarification of the maximum concentration of use for Hamamelis Virginiana (Witch Hazel) Extract in cosmetic formulations.

The Panel also requested confirmation that the only function of Hamamelis Virginiana (Witch Hazel) Flower Water is fragrance ingredient and whether the Research Institute for Fragrance Materials (RIFM) intends to perform a safety assessment thereon.

Alkyl Sultaines

The Panel issued an insufficient data announcement for the following 13 alkyl sultaine ingredients.

Cocamidopropyl Hydroxysultaine
Capryl Sultaine
Cetyl/Lauryl/Myristyl Hydroxysultaine
Coco-Hydroxysultaine
Coco-Sultaine
Erucamidopropyl Hydroxysultaine
Lauramidopropyl Hydroxysultaine
Lauryl Hydroxysultaine
Lauryl Sultaine
Myristamidopropyl Hydroxysultaine
Myristyl Sultaine
Oleamidopropyl Hydroxysultaine
Tallowamidopropyl Hydroxysultaine

The additional data needed are:

- Method of manufacturing for all these ingredients.
- Impurities data for all these ingredients, except for Cocamidopropyl Hydroxysultaine, Lauramidopropyl Hydroxysultaine, and Lauryl Hydroxysultaine
    - If impurities data indicate known sensitizing agents (e.g., 3,3-dimethylaminopropylamine (DMAPA)) are present, additional safety test data may be needed
- Irritation and sensitization data for Capryl Sultaine, Lauryl Sultaine, or Myristyl Sultaine.

144th Meeting Notes

Director's Report

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' support of his promotion to Executive Director and that of Monice Fiume to Senior Director.

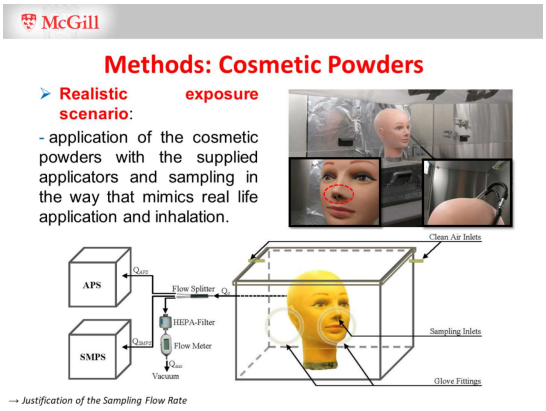
Dr. Heldreth pointed out two cogent presentations made to the Panel at this meeting, and significant discussion involving Aerosols and the other two CIR Precedent documents under review at this meeting. He also discussed the finalized status of the Preliminary Search Engines and Websites information resource document, including its public availability (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites) and the language therein approved for use in CIR reports going forward. This, and all other CIR Findings & Resources Documents, may be found on the dedicated page of the same name (http://www.cir-safety.org/cir-findings).

Dr. Heldreth reminded stakeholders about an impending change of status with regard to 3 ingredients, set for later this year. Specifically, Hydrolyzed Carrageenan and MEA-Hydrolyzed Silk will be moved to the "zero-use category," and Silkworm Cocoon Extract will be moved to the "use not supported" category, if data needs for assessing the safety of these ingredients are not met by the end of this year.

With regard to visibility of CIR, Dr. Heldreth mentioned that since the last Panel meeting, CIR staff made a presentation at a cosmetic science conference in Shanghai, sharing the structure of CIR and the safety assessment process performed herein, with members of the industry in Asia. Additionally, Ms. Fiume will be representing CIR at the upcoming 7th Cosmetic Compliance Conference, in New York, NY, on November 1st (https://cosmeticscompliance.iqpc.com/).

Presentations

At the June 2017 meeting, the Panel requested further expert input on the topic of aerosols and otherwise incidentally inhalable particles. In response, two presentations were made at this meeting. Dr. Yevgen Nazarenko presented a briefing titled "Exposure Assessment of Nanomaterial-Containing Aerosols from Spray and Powder Products." Dr. Nazarenko is currently a Postdoctoral Fellow at McGill University in Montreal, QC, Canada. He presented research that he performed as a graduate student at Rutgers University.

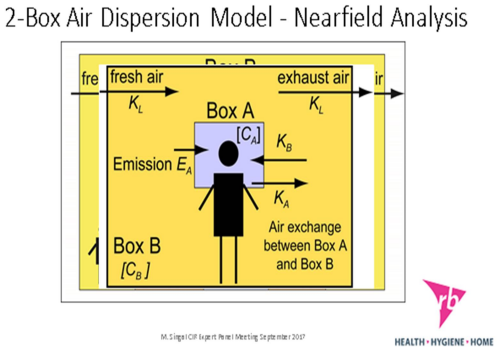


Dr. Nazarenko emphasized the importance of knowing what techniques were used for collecting and preparing samples to characterize aerosols, because airborne particles can agglomerate, and the agglomeration state may be different from what is actually in the air when cosmetic products are used. He also noted the complexity of the dynamics of aerosols after spraying, emphasizing the importance of considering critical factors when evaluating inhalation exposures, including evaporation, condensation, coagulation, and precipitation of the constituents of the aerosolized particles or droplets, as well as temperature, relative humidity, how much is sprayed and how the product is applied.

In his research, Dr. Nazarenko found that nanoparticles can be found in, or released to the air from, cosmetic products, regardless of whether the products are marketed to contain such. He found that many nanoaggregates and nanoagglomerates were released even when energetic sprayers, such as nebulizers, were used to disperse the products to the air. Using a mannequin sampler, he determined that most (85% to 93%) of the mass of inhaled airborne nanoparticles released from powders deposit in the head airways. The inhaled dose of the aerosol fraction above 100 nm was 3 to 8 orders of magnitude greater than the dose of the fraction within the nano range.

Dr. Nazarenko noted that reducing incidental inhalation exposures to nanoparticles from cosmetic products can be accomplished by, for example, using spraying devices, ingredients, and formulations that enable minimizing aerosol generation and the size distributions of the particles released from these products. He emphasized that manufacturers should disclose information needed to ensure the safety of cosmetic products, including information characterizing the size distributions of the particles and droplets emanating from products, when used as intended, as well as factors such as the identities and concentrations of the ingredients in the cosmetic formulations.

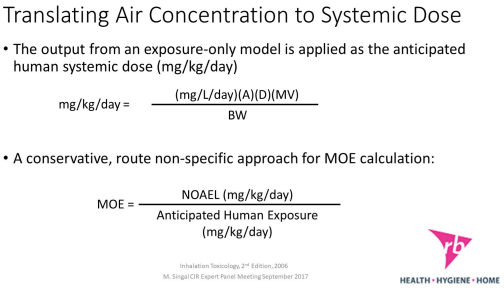
Dr. Madhuri Singal then presented a briefing titled "Considerations for Inhalation Safety Assessment: Approaches and Application." She is an Inhalation Toxicologist and Senior Consumer Safety Associate at Reckitt Benckiser, LLC, in Parsippany, NJ.



Dr. Singal opened her presentation with an example illustrating the importance of considering the scale of the data used to assess the safety of ingredients in cosmetic products that may be incidentally inhaled. Data can easily be misinterpreted when evaluated without properly considering the critical context provided by the scale of the measurements used in the analysis.

Dr. Singal emphasized the need to understand the distinct characteristics of each product evaluated. She noted that integral factors in inhalation exposure and safety assessments include the concentrations of the ingredient of interest in the spray formulation and an understanding of the chemical and biological properties of the ingredient and how the spray device releases the formulation to the air, as well as the airborne concentration of the ingredient, the spray rate, the air exchange rate of the room in which the product is used, and physiological factors, including respiratory rate, tidal volume, and clearance mechanisms. She explained the importance of considering the solubility and surface charge and, especially, the chemical reactivity of the ingredient in safety assessments wherein inhalation is a potential route of exposure.

Dr. Singal described several computational tools available for assessing the exposure, deposition, and bioavailability of incidentally inhaled particles and droplets, including the 2-Box Air Dispersion model, which is depicted, conceptually, in the figure above. She mentioned that the near-field analysis capability of this model would be most relevant in cosmetic ingredient safety assessments, centered on the head, but the model can be adjusted to evaluate, for example, whole-body near-field exposures and far-field exposures, as necessary. All of these models can be used to estimate exposures in defined conservative consumer or occupational exposure scenarios. In addition, all of them are amenable calculating refined estimates of exposures based on real-world measurements that reflect more accurately than the default assumptions the actual exposure scenarios of interest. And, once a modeled exposure concentration is obtained, it is necessary to calculate dose (mg/kg/day) to calculate an MOE.



Dr. Singal discussed the Multiple Path Particle Deposition (MPPD) Model, in particular, indicating that refinements of this model have enabled quantitatively estimating the amount of an ingredient that will be deposited in each of the three major regions of the respiratory tract, including the head airways, tracheobronchial region and alveolar region, when a cosmetic spray or powder product is used as intended. She emphasized that this model can estimate respiratory tract deposition in children as young as 3 months of age, as well as in older individuals.

Other Items: Precedents (Guidance Documents) and Re-Review Summaries

CIR Precedents (Guidance Documents):

Aerosols

The CIR Precedents – Aerosols Document was updated to address some of the comments received on the previous draft, including the April 3, 2017 comments from Women's Voices for the Earth (WVE), and the revised document was submitted to the Panel in anticipation of presentations by Drs. Nazarenko and Singal. As noted above, the presentations at the September 2017 meeting addressed exposure assessment of nanomaterial-containing aerosols from cosmetic spray and powder products and considerations for inhalation safety assessments. The Panel concluded that the document must be revised to include information presented by these speakers and comments received on the document to date. In addition, the document should be corrected to replace the assumption that 5% of the particle-size distribution released from propellant deodorant sprays consist of respirable particles with the assumption that 50% of the particles are respirable. In addition, the Panel recommended that the cosmetics industry perform an empirical study to characterize the particle-size distributions released from an adequate number of representative cosmetic propellant and pump spray products using current tools and methods.. The Panel emphasized Dr. Nazarenko's observation that there are substantial analytical-method platform-dependent differences in particle-size measurements, which the Panel will need to consider in the future when evaluating the nature and the quality of the data used to assess the safety of ingredients in cosmetic formulations that may be incidentally inhaled. Finally, the Panel noted that after all these data are collected and analyzed, and the precedents document finalized, the updated language is intended to apply to previous as well as future CIR safety assessments..

Endocrine Activity

The Panel reviewed the second draft of the CIR Expert Panel Endocrine Activity and Endocrine Disruption Background and Framework document, which was revised to address comments on the first draft received from the Council, the CIR Science and Support Committee (CIR SSC), and from Dr. Ellen Mihaich. (Dr. Mihaich briefed the Panel on the subject of endocrine activity and disruption at the December 2016 Panel meeting.) Overall, the Panel was pleased with the document. The final version of the CIR Precedents – Endocrine Activity Document is available on the CIR Findings & Resources Documents page (http://www.cir-safety.org/cir-findings).

Hair Dye Epidemiology

The Panel reviewed the latest draft of the Hair Dye Epidemiology document. The previous draft was reviewed by the Panel at the April 2017 meeting. Comments on the previous draft that were received from the Council Hair Coloring Technical Committee (HCTC) and from the Panel were addressed. The Panel noted that a presentation on hair dye self-testing and hair dye chemistry is scheduled for the December 2017 Panel meeting. The Panel approved the current revisions, but tabled the document pending the presentation in December. The Panel noted that summaries of two recently published epidemiological studies suggest an association between hair dye use and the incidence of breast carcinoma. The Panel concluded that summaries of other, older epidemiological studies that have examined this association should be included in the document as well.

Re-Review Summaries:

Glyoxal

The Panel approved the re-review summary of Glyoxal with the conclusion that it is safe for use in products intended to be applied to the nail at concentrations ≤ 1.25%, and that the available data are insufficient to support the safety for other uses.

The Panel has now reviewed information that has become available since the year 2000 assessment, along with updated information regarding product types, and frequency and concentrations of use. The Panel determined to not reopen this safety assessment and reaffirmed the conclusion published in 2000. The Panel also noted that suppliers should take steps to limit the concentration of the free formalin impurity to 0.2% (0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol), which is consistent with the 2013 CIR safety assessment of Formaldehyde and Methylene Glycol.

Quaternium-26

The Panel approved the re-review summary of Quaternium-26 with the conclusion that it is safe as used in cosmetic products.

Unlike the current exclusive use of Quaternium-26 in non-coloring hair products (16 rinse-off and 10 leave-on reported uses), data in the final report that was published in 2000 indicated use in this product type as well as in cleansing skin care preparations and bath soaps and detergents. The difference in Quaternium-26 use frequency is not significant when data in the published final report are compared with current data (i.e., 25 uses and 26 uses, respectively). According to the published final report from 2000, Quaternium-26 was being used at concentrations up to 5%. However, the results of a concentration of use survey that was conducted by the Council in 2015-2016 indicated that Quaterium-26 is being used at maximum concentrations up to 2% in rinse-off products (hair conditioners) and maximum concentrations up to 0.15% in leave-on products (tonics, dressings, and other hair grooming aids).

Biotin

The Panel approved the re-review summary of Biotin with the conclusion that it is safe as used in cosmetics.

Some new data were identified in the published literature; these data were similar to data that were included in the original assessment. The Panel reviewed updated information regarding product types and ingredient use frequencies provided by the FDA and maximum use concentrations provided by the Council. The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion.

The reported frequency of use of Biotin in cosmetics has increased since its safety was originally reviewed; 71 uses were reported 1998, and 506 uses are reported in 2017. The reported maximum leave-on concentration of use has decreased from 0.6% to 0.1%. The number of uses in formulations with intentional application near the eye area increased from 2 to 54, and the maximum concentration of use reported for this type of exposure increased from 0.01% to 0.1%. However, this use concentration is still quite low, and did not raise any new concerns.

As in the original assessment, the Panel recognized that data on the irritation and sensitization potential of Biotin were absent. However, the Panel was of the opinion that if Biotin had a strong potential for irritation or sensitization, case reports would be available in the published literature.

The Panel also noted that there are reproductive studies of Biotin that show strong inhibition of spermatogenesis. However, these are oral studies at high levels which are irrelevant to uses in cosmetics. Therefore, it is the opinion of the Panel that the results of those studies are not pertinent to the safety of Biotin as a cosmetic ingredient.

Scientific Literature Reviews

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

- Alkoxylated Fatty Amides
- Cyclic Polyol Phosphates
- *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients
- *Ginkgo biloba*-Derived Ingredients
- *Glycine soja* (Soy)-Derived Ingredients
- *Melaleuca alternifolia* (Tea Tree)-Derived Ingredients
- Zinc Salts

Next CIR Expert Panel Meeting

Monday and Tuesday, December 4-5, 2017, at the Darcy Hotel, Washington, DC.
Please contact Carla Jackson (jacksonc@cir-safety.org) before the meeting if you plan to attend.