Post Meeting Announcement

Cosmetic Ingredient Review Expert Panel
145th Meeting (December 4-5, 2017) - Findings

December 8, 2017

● Final Safety Assessments

- **Ammonia and Ammonium Hydroxide – 2 ingredients – Split conclusion (safe with qualifications in each)**
- **Persulfates – 3 ingredients – Split conclusion**
- **Polysilsesquioxanes – 18 ingredients – Safe as used**
- **Triglycerides – 51 ingredients – Safe as used**
- **Panthenol, Pantothenic Acid, and Derivatives – 7 ingredients – Safe as used**

● Tentative Safety Assessments

- **Malic Acid and Sodium Malate – 2 ingredients – Safe as used**
- ***Mentha piperita* (Peppermint)-Derived Ingredients – 10 ingredients – Split conclusion**
- **Alkyl Sultaines – 13 ingredients – Safe as used**
- **Zinc Salts – 27 ingredients – Safe with non-irritating caveat**
- **Alkane Diols – 10 ingredients – Split conclusion**
- ***Hamamelis virginiana* (Witch Hazel)-Derived Ingredients – 8 ingredient – Safe with non-irritating and non-sensitizing caveats**

● Insufficient Data Announcements

- ***Ginkgo biloba*-Derived Ingredients – 10 ingredients**
- ***Eucalyptus globulus* (Eucalyptus)-Derived Ingredients – 6 ingredients**

● Tabled Assessment

- **Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) – 1 ingredient**

● 145th Meeting Notes

- **Director's Report**
- **Presentations**
- **Other Item**
  - **Precedents (Guidance Document)**
- **Scientific Literature Reviews under development**
- **Next Expert Panel Meeting – Monday and Tuesday, March 5-6, 2018**

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 Unpublished data cited as references in CIR safety assessments are available for review.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.

Ammonia and Ammonium Hydroxide

The Cosmetic Ingredient Review Expert Panel (Panel) issued a final report with the conclusion that Ammonia and Ammonium Hydroxide are safe as used in hair dyes and colors, and safe in cosmetics applied directly to the skin 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 (which is also used as a denaturant) 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).

Because the use of hair dyes can be irritating, the Panel stated that skin contact should be minimized when using such products.

Persulfates

The Panel issued a final amended report with the conclusion that Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and hair lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. The Panel also concluded that the available data are insufficient for determining the safety of these ingredients in leave-on products and dentifrices.

The additional data needed to evaluate the safety of these ingredients in leave-on products and dentifrices are:

- No-Observed-Adverse Effect-Level (NOAEL) for sensitization and urticarial reactions
- Concentrations of use in leave-on products and dentifrices.

The data needs stated above are the same as those issued at the June 2017 meeting and no data have been received in response thereto. Regarding the "safe as used" part of the current conclusion (stated above), "in hair colorants and lighteners" was changed to "in hair colorants and hair lighteners" to clarify that this conclusion did not apply to skin lighteners.

Specific to dentifrices, the Panel learned of an FDA public health notification concerning the risk of allergic reactions in users of denture cleansers containing Sodium Persulfate, and the risks of misusing these products, prior to initially determining the data needed for completion of this safety assessment. The Panel determined that not enough information (e.g., maximum concentration of use) had been provided to determine the safety of these ingredients for this use. As with toothpastes and mouthwashes, cosmetic use of dentifrices is only applicable in the absence of formulation with fluoride.

Polysilsesquioxanes

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

Acryloyloxypropyl Polysilsesquioxane*
C26-28 Alkyldimethylsilyl Polypropylsilsesquioxane*
C30-45 Alkyldimethylsilyl Polypropylsilsesquioxane
Dimethicone/Silsesquioxane Copolymer
Dimethiconol/Caprylylsilsesquioxane/Silicate Crosspolymer*
Ethyl Polysilsesquioxane*
Hydrogen Dimethicone/Octyl Silsesquioxane Copolymer
Isobutyl/Methoxy PEG-10 Polysilsesquioxane*
Isobutyl Polysilsesquioxane*
Methacryloyloxypropyl Polysilsesquioxane*
Methoxy PEG-10 Polysilsesquioxane*
Polycaprylylsilsesquioxane
Polymethylsilsesquioxane
Polydimethylsiloxy PEG/ PPG-24/19 Butyl Ether Silsesquioxane
Polydimethylsiloxy PPG-13 Butyl Ether Silsesquioxane*
Polymethylsilsesquioxane/Trimethylsiloxysilicate*
Polypropylsilsesquioxane
Trimethylpentyl Polysilsesquioxane*

**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 a lack of systemic toxicity data (i.e. reproductive and developmental toxicity and carcinogenicity data), but agreed that these ingredients are large, insoluble molecules that share dominant features/structures, and are not expected to penetrate the skin. The Panel also agreed that the weight of the evidence alleviated concerns about the potential for local effects, such as dermal irritation and sensitization. This was reinforced by newly submitted data that included acute oral toxicity, genotoxicity, and dermal irritation on additional ingredients. However, manufacturers should use current good manufacturing practices to ensure that the levels of monomers and source materials are minimized in the final products.

Polymethylsilsesquioxane was reported to be used in 397 formulations, i.e., 374 in leave-on formulations, 22 in rinse-off formulations, and 1 diluted for the bath formulation. All other ingredients reportedly in use were specified to be used in 14 formulations or fewer. Polymethylsilsesquioxane has the highest reported

maximum concentration of use; it is used at up to 55.2% in the category of other makeup preparations. The rest of the ingredients reportedly in use were stated to be used at 4.9% (e.g., C30-45 Alkyldimethylsilyl Polypropylsilsesquioxane in foundations) or less.

Triglycerides

The Panel issued a final amended report 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.*

The ingredients listed in blue were previously reviewed by the Panel. The conclusion reached by the Panel at this meeting reaffirmed the original conclusions of safety.

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook*, a reported potential function of Docosahexenoic/ Docosapentenoic/Oleic/Palmitic Triglyceride is as a skin bleaching agent. However, in the U.S., skin bleaching agent is not considered a cosmetic function, and therefore use in that manner was not assessed in this report.

Finally, the Panel recognized that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals. Therefore, 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.

Panthenol, Pantothenic Acid, and Derivatives

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

Panthenol
Pantothenic Acid
Panthenyl Ethyl Ether
Panthenyl Ethyl Ether Acetate*
Panthenyl Triacetate
Calcium Pantothenate
Sodium 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 also noted that these ingredients may contain residual amine impurities, and thus cautioned that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

Panthenol, Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, and Panthenyl Triacetate can be metabolized to Pantothenic Acid, an essential nutrient. The Panel recognized that exposures from absorbed amounts of these compounds are below what would be typical from dietary intake, thereby underscoring the safety of the ingredients.

Tentative Safety Assessments

*Tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before **December 15, 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 as early as at its **March 5-6, 2018** meeting.*

Malic Acid and Sodium Malate

The Panel issued a tentative amended report for public comment with the conclusion that Malic Acid and Sodium Malate are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The Panel noted that there are no sensitization data for Malic Acid at the maximum leave-on use concentration of 2.1%. The results of a human repeated insult patch test (HRIPT) found that Malic Acid at 1% in formulation did not induce dermal sensitization. Based on the experience of the clinicians on the Panel and the fact that Malic Acid and Sodium Malate are common chemicals in human biology, the Panel concluded that these ingredients would not induce sensitization at use concentrations.

The Panel also noted that Malic Acid is an ocular irritant and use as a hair spray has been reported. The Panel thus advises consumers to minimize incidental ocular exposure to hair sprays containing Malic Acid.

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

The Panel issued a revised tentative amended report for public comment with a conclusion that 7 of the 10 *Mentha piperita* (peppermint)-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:

Mentha Piperita (Peppermint) Oil
Mentha Piperita (Peppermint) Extract
Mentha Piperita (Peppermint) Leaf
Mentha Piperita (Peppermint) Leaf Cell Extract*
Mentha Piperita (Peppermint) Leaf Extract
Mentha Piperita (Peppermint) Leaf Juice*
Mentha Piperita (Peppermint) Leaf Water

**Not reported to be in 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 also concluded that the available data are insufficient to make a determination of safety for Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract, Mentha Piperita (Peppermint) Flower/Leaf/Stem Water*, and Mentha Piperita (Peppermint) Meristem Cell Culture*. (**Not reported to be in use.*)

The following data needed to formulate a conclusion of safety:

- 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

At the September 2017 Panel meeting, the Panel issued a tentative amended conclusion stating that Mentha Piperita (Peppermint) Oil is safe in the present practices of use and concentration when formulated to be non-sensitizing, but that the available data were insufficient for making a determination of safety for the remaining 9 ingredients. A revised tentative amended report is being issued at this meeting because the Panel determined that the data on Mentha Piperita (Peppermint) Leaf Extract and Mentha Piperita (Peppermint) Extract that were received in response to the data needs associated with the insufficient data conclusion support the safe use of Mentha Piperita (Peppermint) Extract, Mentha Piperita (Peppermint) Leaf, and the 4 ingredients that are derived from the leaf, when these ingredients are formulated to be non-sensitizing. However, the available data remain insufficient for making a determination of safety in cosmetic products for Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract, Mentha Piperita (Peppermint) Flower/Leaf/Stem Water, and Mentha Piperita (Peppermint) Meristem Cell Culture.

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.

Alkyl Sultaines

The Panel issued a tentative report for public comment with the conclusion that the following 13 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

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

**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 expressed concern that 3,3-dimethylaminopropylamine (DMAPA) and related amines that may exist as impurities in the amidopropyl hydroxysultaine ingredients could cause sensitization. Dermal sensitization was not observed in animal or human studies of Cocamidopropyl Hydroxysultaine and Lauramidopropyl Hydroxysultaine and suppliers have reported that DMAPA impurities are at extremely low levels (< 3 ppm). To ensure that sensitization does not occur in consumers, the Panel urges manufacturers to minimize the content of DMAPA and related sensitizing agents in cosmetic formulations.

Zinc Salts

The Panel issued a tentative report for public comment with the conclusion that the 27 zinc salts listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

Zinc Acetate
Zinc Ascorbate
Zinc Ascorbate Hydroxide*
Zinc Aspartate
Zinc Carbonate
Zinc Carbonate Hydroxide*
Zinc Chloride
Zinc Chloride Hydroxide*
Zinc Citrate
Zinc Cysteinate*
Zinc Gluconate
Zinc Glutamate*
Zinc Glycinate
Zinc Hexametaphosphate*
Zinc Hydroxide
Zinc Lactate
Zinc Laurate
Zinc Myristate
Zinc Neodecanoate*
Zinc Nitrate*
Zinc Palmitate*
Zinc Phosphate
Zinc Ricinoleate
Zinc Salicylate
Zinc Stearate
Zinc Sulfate
Zinc Undecylenate

**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 Scientific Literature Review (SLR) that was issued for this group of ingredients included Zinc Sulfide. Because Zinc Sulfide is chemically different from the other ingredients included in this safety assessment (e.g., is not a dissociable salt), the Panel removed Zinc Sulfide from the report.

The majority of the zinc salts are not reported to be irritating. However, because irritation was reported in testing with 1% Zinc Chloride and the threshold for irritation is not known, the Panel specified that products containing zinc salts must be formulated to be non-irritating.

The Panel noted that Zinc Sulfate reduced hair shaft melanin content in an oral exposure study, and that hair shaft depigmentation was observed during multiple hair cycles in treated animals. However, the Panel noted that this study was conducted at high concentrations and therefore the results were not toxicologically significant to the safety of use in cosmetics.

Alkane Diols

The Panel issued a revised tentative report for public comment, with a split conclusion of safety for this ingredient family. The Panel concluded that the following 7 (of 10 total) alkane diols are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Butyl Ethyl Propanediol
1,10-Decanediol
Hexanediol
Isopentyldiol
Methylpropanediol
1,5-Pentanediol*
Propanediol

**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 also determined that the data are insufficient to determine the safety of 1,4-Butanediol, 2,3-Butanediol (not reported to be in current use), and Octanediol for use in cosmetic formulations.

Concentration of use data are needed to evaluate the safety of 1,4-Butanediol. Because 1,4-Butanediol can be metabolized into gamma-hydroxybutyric acid (GHB), a controlled substance in the United States, and because maximum reported concentrations of use are as high as 40%, the Panel stated that it is necessary to have this data in order to determine safety for use in cosmetic formulations.

For 2,3-Butanediol and Octanediol, the following data are needed:

- Concentration of use
- 28-Day dermal toxicity studies
- Developmental and reproductive toxicity data
- Mammalian genotoxicity studies (if these ingredients are used at low concentrations, these data may not be needed)

In the previous tentative report, 1,5-Pentanediol was listed as having insufficient data. However, because the report includes metabolism data, acute oral toxicity data, negative Ames test data, and negative irritation, sensitization, and photosensitization data, the Panel determined that the data were no longer considered insufficient.

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

The Panel issued a tentative report with the conclusion that the following 8 *Hamamelis virginiana* (witch hazel)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing.

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 Panel's concerns included the presence of geraniol and the oxidation products of linalool in cosmetics, which could result in potential dermal sensitization, as well as other constituents of concern. At the reported concentrations of use of these *Hamamelis virginiana* (witch hazel)-derived ingredients, the constituents that may cause these effects are present far below levels of concern, including for sensitization. However, 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. Also, these ingredients are astringents and are reported to be used in products used around the eyes, thus, may be irritating.

Hamamelis Virginiana (Witch Hazel) Water is reported to be used in 386 formulations (255 in leave-on formulations, 122 in rinse-off formulations, and 9 in formulations that are diluted for the bath). Hamamelis Virginiana (Witch Hazel) Extract is reported to be used in 359 formulations and Hamamelis Virginiana (Witch Hazel) Leaf Extract is reported to be used in 218 formulations. All other in-use ingredients are reported to be used in 128 or fewer formulations. Hamamelis Virginiana (Witch Hazel) Water has the highest reported maximum concentration of use; it is used at up to 43% (in the category of other skin care preparations). All other in-use ingredients are reported to be used at up to 4.3% or less.

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 as soon as at its* ***March 5-6, 2018*** *meeting.*

***Ginkgo biloba*-Derived Ingredients**

The Panel issued an Insufficient Data Announcement (IDA) for the following ingredients:

Ginkgo Biloba Leaf Extract
Ginkgo Biflavones
Ginkgo Biloba Leaf
Ginkgo Biloba Leaf Cell Extract
Ginkgo Biloba Leaf Powder
Ginkgo Biloba Leaf Water
Ginkgo Biloba Meristem Cell
Ginkgo Biloba Nut Extract
Ginkgo Biloba Root Extract
Ginkgo Leaf Terpenoids

The data needed for these cosmetic ingredients are:

- Method of manufacturing for each of these *Ginkgo biloba*-derived **cosmetic ingredients**
- Composition and impurities data for each of these *Ginkgo biloba*-derived **cosmetic ingredients**
- 28-Day dermal toxicity data
- Dermal irritation and sensitization data at leave-on use concentrations
- Ocular irritation data, if available
- Genotoxicity data
- Developmental and reproductive toxicity data

- Data on the absorption spectra or phototoxicity of these **cosmetic ingredients**

***Eucalyptus globulus* (Eucalyptus)-Derived Ingredients**

The Panel issued an IDA for the following *Eucalyptus globulus*-derived ingredients.

Eucalyptus Globulus Leaf	Eucalyptus Globulus Leaf Powder
Eucalyptus Globulus Leaf Extract	Eucalyptus Globulus Leaf/Twig Oil
Eucalyptus Globulus Leaf Oil	Eucalyptus Globulus Leaf Water

The data needs are:

- Sensitization on Eucalyptus Globulus Leaf Oil at 5.5% or greater
- Impurity data on all ingredients
- Margin of safety (MOS) calculations for inhalation and dermal exposure using the Eucalyptus Globulus Leaf Oil and/or the major constituent, eucalyptol (1,8-cineole)

Tabled Assessment

For this tabled assessment, 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****.*

Polyaminopropyl Biguanide (aka polyhexamethylene biguanide hydrochloride)

The draft final report on this ingredient was tabled in response to a commitment from the cosmetics industry to complete a 100-person human repeated insult patch test of a product containing Polyaminopropyl Biguanide. The task force that will be overseeing this project is being formed, and the Panel will receive ongoing updates relating to this project. The Panel requested that a progress report be given at the March 2018 Panel meeting.

At the September 2017 Panel meeting, 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 μg/cm^2 (and recommend to test at 500 μg/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 μg/cm^2, which theoretically supports the use of this ingredient at concentrations of ≤ 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 (> 100 subjects) on a more diverse study population at a dose of 500 and 1000 μg/cm^2 is needed to derive an acceptable NESIL.

Additionally, a letter expressing concern about the inhalation toxicity potential of Polyaminopropyl Biguanide was received from Women's Voices for the Earth (WVE) prior to this Panel meeting. According to this communication, the results of an internet search yielded a number of cosmetic products whereby inhalation is a route of exposure. These products were not identified specifically in 2017 FDA Voluntary Cosmetic Registration Program (VCRP) data on Polyaminopropyl Biguanide, however, CIR indicated in the use table that some of the product types reported to the VCRP may be sprays or powders, but it is not known if they are sprays or powders. The CIR Executive Director will develop an appropriate response to WVE's concerns.

145th Meeting Notes

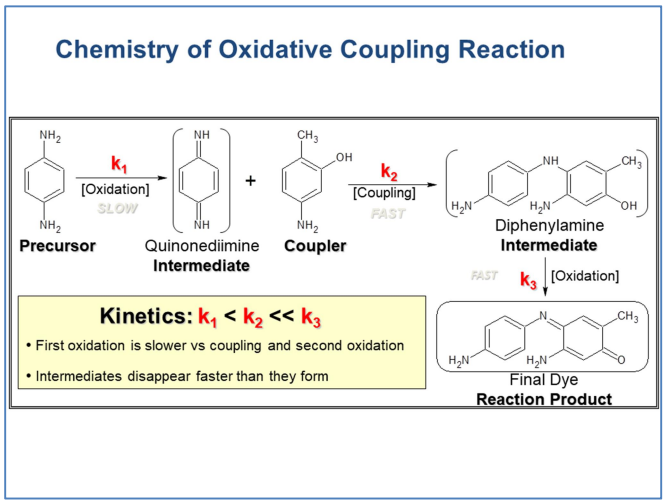
Director's Report

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continuing support of Cosmetic Ingredient Review program.

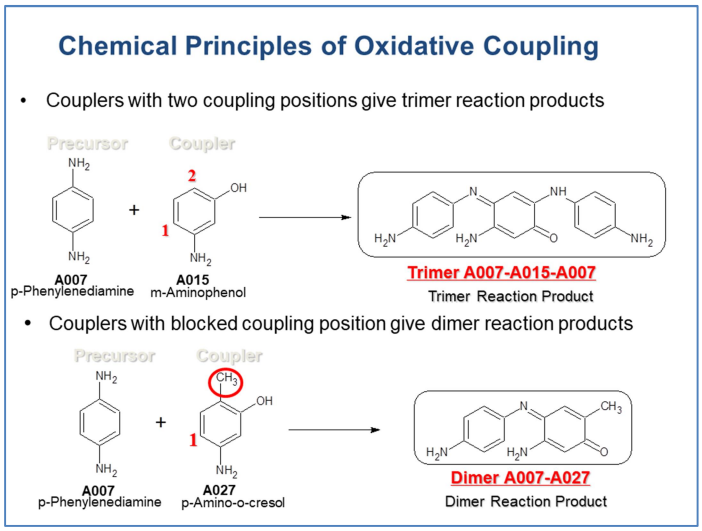
Dr. Heldreth thanked the appropriate parties for two cogent presentations made to the Panel at this meeting, and the significant discussion involving issues associated with hair dyes. He also discussed the finalized status with regard to 3 ingredients that had previously been classified as having insufficient data. Specifically, Hydrolyzed Carrageenan and MEA-Hydrolyzed Silk have been moved to the "zero-use category," and Silkworm Cocoon Extract has been moved to the "use not supported" category.

With regard to visibility of CIR, Dr. Heldreth mentioned that since the last Panel meeting, Ms. Fiume made a presentation at the 7th Cosmetic Compliance Conference, in New York, NY, in November, sharing the structure of CIR and the safety assessment process performed herein (https://cosmeticscompliance.iqpc.com/).

Presentations

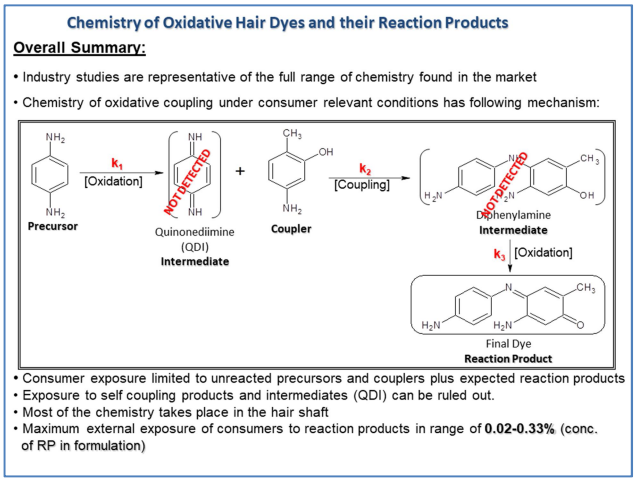


The Panel requested further expert input on the topics of hair dye chemistry and allergy testing. In response, two presentations were made at this meeting. Dr. Carsten Goebel presented a briefing titled "Chemistry of Coloring." Dr. Goebel is currently responsible for the safety evaluation of the professional hair care division at Coty.

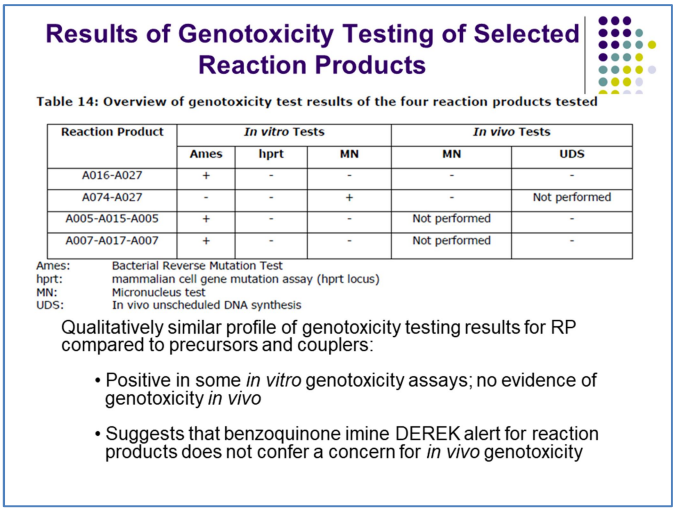


Dr. Goebel emphasized that the safety assessment of oxidative hair dyes is driven by the toxicological evaluation of the ingredients (i.e., precursors and couplers) rather than by the reaction products formed during use. In his presentation, reaction products were identified and quantified, determined to represent extremely low relative exposure, and demonstrated no evidence of *in vivo* genotoxicity.

Therein, he demonstrated that common precursors and couplers and precursors used in oxidative hair dye formulations. And, Dr. Goebel showed the common reaction pathways and reaction products, resulting in dimer and trimer products.



According to Dr. Goebel, consumer exposure is limited to unreacted precursors and couplers, plus expected reaction products. He stressed that self-coupling products and intermediates can be ruled out and that the maximum external exposure to reaction products is in the range of 0.02 to 0.33% (concentration in formulation).



Finally, Dr. Goebel detailed the results of various *in vitro* and *in vivo* genotoxicity tests on oxidative hair dye reaction products. DEREK alerts had indicated that some of these products had the potential for positive genotoxicity. However, even though Ames and micronucleus tests seemed to concur with these alerts in some cases, none of the *in vivo* test results were indicative of genotoxicity.

Main conclusions of the study

- Open testing under realistic hair dye use conditions (AAT design) was efficient to cause a reaction noticeable by the majority of study subjects (39/42 subjects available for analysis) within 48 hours. This was objectified by dermatological evaluation. In addition, the dermatological evaluation did not find significant differences between Day 2 and Day 4. Therefore, a self-evaluation period of 2 days is feasible.
- Comparison of the two test sites (response rate of 90.5% on forearm and 93% behind the ear) did not reveal statistically significant differences, both by self-assessment and when combined with dermatological assessment.
- All subjects (19/19) with the highest reactivity to PPD (+++) reacted already to PPD concentrations between 0.05 and 0.75% in the AAT, indicationg that they would be adequately alerted to avoid hair dyeing.

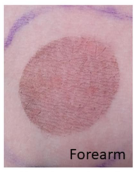
The results of this study demonstrated that an alternative test methodology (alternative to the standard hair dye patch test) could adequately alert consumers with hair dye allergies to avoid hair dyeing, but very importantly, tested in a location that is easier to self-assess (forearm as opposed to behind the ear) and tested with a much shorter exposure time (45 minutes as opposed to 24 hours in the standard patch test). Potentially, this shorter exposure time might result in a reduced potential to self-sensitize the consumer with the test itself.

Dr. Maya Krasteva then presented a briefing titled "Allergy Alert Test: Proof of Concept Study." Dr. Krasteva is a Eurotox registered dermatologist and is currently a Senior Scientist at L'Oreal, involved with safety evaluation, post-marketing safety, and regulatory affairs. Dr. Krasteva emphasized that in the results of this study on hair dye allergy alert testing, there were no statistically significant differences between 1) consumer self-assessment and dermatological assessment, 2) testing site results behind the ear or on the forearm, and 3) assessment between day 2 or day 4. She also concluded that these new parameters for hair dye allergy testing would adequately alert consumers with allergies to hair dye ingredients to avoid hair dyeing.

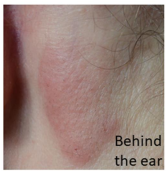
Case study: Subject AU01

- 21 year-old male
- Declared a reaction to a dark shade in real use conditions (mean concentration 0.75% PPD)
- Severity of clinical reaction: mild
- Patch test to PPD (2012): weakly positive (+)
- Noticed 14.5 hours post-AAT reactions developing on both sites to Product C (0.75%): reddening and itching; swelling dveloped later.

Reactions to Product C (0.75% PPD), Day 2



Overall grade: Moderately positive
Total score: 12
Involved area: 90 - 100%
Involvement: homogeneous
Strength: medium
Papules/infiltration: many
Vesicles: 0
Itching: yes



Overall grade: Strongly positive
Total score: 15
Involved area: > 100%
Involvement: homogeneous
Strength: strong
Papules/infiltration: homogeneous infiltration
Vesicles: 0
Itching: yes

Other Item: CIR Precedent (Guidance Document)

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 September 2017 meeting. Comments on the previous draft were addressed and a few additional studies were added to the document. The Panel noted the presentations on hair dye self-testing and hair dye chemistry at this meeting. The Panel approved the current revisions. However, the Panel concluded that the services of an expert epidemiologist, with experience specifically relevant to factors associated with breast cancer, should be retained. Specifically, this expert would be asked to evaluate all of the currently available epidemiology studies that investigated the potential association between hair dye use and breast cancer, reconcile the disparities in the results of those studies, and provide the Panel with a concise summary for inclusion in this Precedents document.

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
- Fatty Acids and Soaps
- Fluoropolymers
- Hydrogen Peroxide
- *Melaleuca alternifolia* (Tea Tree)-Derived Ingredients
- Triphenyl Phosphate
- *Glycine soja* (Soy)-Derived Ingredients

Next CIR Expert Panel Meeting
Monday and Tuesday, March 5-6, 2018, at the Darcy Hotel, Washington, DC.
Please contact Carla Jackson (jacksonc@cir-safety.org) before the meeting if you plan to attend.