Post Meeting Announcement

Cosmetic Ingredient Review Expert Panel
146th Meeting (March 5-6, 2018) - Findings

March 9, 2018

● Final Safety Assessments

- **Alkane Diols – 10 ingredients – Split conclusion (safe as used for 7; insufficient data for 3)**
- **Malic Acid and Sodium Malate – 2 ingredients – Safe as used**
- ***Mentha piperita* – 10 ingredients – Split conclusion (safe with qualifications for 7; insufficient for 3)**
- **Alkyl Sultaines – 13 ingredients – Safe as used**
- **Zinc Salts – 27 ingredients – Safe with qualifications**
- ***Hamamelis virginiana* – 8 ingredients – Safe with qualifications**

● Tentative Safety Assessments

- ***Eucalyptus globulus* – 6 ingredients – Safe with qualifications**
- ***Ginkgo biloba* – 10 ingredients – Insufficient data conclusion**
- **Triphenyl Phosphate – 1 ingredient – Safe as used**

● Insufficient Data Announcements

- **Polyfluorinated Polymers – 12 ingredients**
- **Polyol Phosphates – 10 ingredients**

● 146th Meeting Notes

- **Director's Report**
- **Presentation**
- **Other Items**
  - **Parabens – 21 ingredients – Insufficient data**
  - **Draft 2019 Priorities**
  - **Re-Review Strategy – Acrylates Copolymer**
- **Scientific Literature Reviews under development**
- **Next Expert Panel Meeting – Monday and Tuesday, June 4-5, 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 Unpublished data cited as references in CIR safety assessments are available for review.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.

Alkane Diols

The CIR Expert Panel (Panel) issued a final report, with a split conclusion of safety for this ingredient family. The Panel concluded that the following 7 alkane diols are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

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

**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 determined that the data are insufficient to determine the safety of 1,4-Butanediol, 2,3-Butanediol,** and Octanediol for use in cosmetic formulations.

***Not reported to be in current use. Ingredients in this group with no reported uses and a final insufficient data conclusion are hereby moved to the "Insufficient Data – No Reported Uses" category.*

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, 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
- dermal and reproductive toxicity data
- Mammalian genotoxicity studies

Furthermore, the Panel noted that 2,3-Butanediol was metabolized to diacetyl in rats; diacetyl produces pulmonary toxicity with inhalation exposures. However, the exposure to diacetyl via metabolism would not be the same as that from direct inhalation. Because the route of exposure would be different, and because the concentrations of use of 2,3-Butanediol in cosmetics were not provided, the Panel could not assess the risk of this metabolite.

Malic Acid and Sodium Malate

The Panel issued a final amended report 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 conclusion of this report supersedes the one found in the 2001 report.

Overall, the Panel considered that the available data, including the role of Malic Acid in normal metabolism and animal toxicity data, were adequate to assess the safety of these ingredients as used in cosmetics. The Panel noted that in formulation, a pH-dependent equilibrium exists between Malic Acid and its salts; thus, the safety profile between Sodium Malate would not differ from Malic Acid. The Panel also noted that there are no sensitization data for Malic Acid at the maximum leave-on use concentration of 2.1%. The results of an 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 noted that the only significant toxic effect of Malic Acid was irritation to the skin and eyes, which would be expected for acids. Since Malic Acid is used as a pH adjuster in cosmetics, the irritating property of the acid would be minimized in formulated products. The Panel also noted that use of Malic Acid in a hair spray has been reported. The Panel thus advises consumers to minimize incidental ocular exposure of hair sprays containing Malic Acid.

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

The Panel issued a final amended report with a conclusion stating that the following 7 (of 10 total) *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 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 product formulation may each contribute to the final concentration of a single shared constituent. Therefore, when formulating products, manufacturers should avoid reaching concentrations of botanical constituents that may cause sensitization or other adverse effects.

The Panel also concluded that the available data are insufficient to make a determination of safety for 3 of the 10 *Mentha piperita* (peppermint)-derived ingredients. These 3 ingredients, and the data that are needed to complete this safety assessment, are:

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

***Not reported to be in current use. Ingredients in this group with no reported uses and a final insufficient data conclusion are hereby moved to the "Insufficient Data – No Reported Uses" category.*

The data needed to formulate a conclusion of safety for these 3 ingredients comprise:

- 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

Alkyl Sultaines

The Panel issued a final report with the conclusion that the following 13 alkyl sultaines 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 sultaines are structurally related to betaines and are sometimes referred to as sulfobetaines. Each of the ingredients named in this report is a sulfopropyl quaternary ammonium salt. The Panel noted gaps in the available safety data for some of the alkyl sultaines in this safety assessment. Because of structural similarities among the ingredients in the report, data on some of the ingredients can be used to support the safety of ingredients for which no data are available.

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). The Panel noted that the manufacturing processes for each of the amidopropyl hydroxysultaine ingredients are generally similar and are expected to produce the same impurities. In quantitative risk assessments (QRAs) submitted to support the safety of Cocamidopropyl Betaine and related fatty acid amidopropyl betaines, conservative weight-of-evidence (WoE) no expected sensitization induction levels (NESILs) were calculated to be 425 $\mu g/cm^2$ for DMAPA. Based on 1) this NESIL, 2) the lack of reported sensitization to the amidopropyl hydroxysultaine ingredients in the literature, and 3) the use concentrations of the these ingredients, DMAPA would likely be well below doses expected to induce sensitization; however, 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 final report 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 Cysteinate*	Zinc Neodecanoate*
Zinc Ascorbate	Zinc Gluconate	Zinc Nitrate*
Zinc Ascorbate Hydroxide*	Zinc Glutamate*	Zinc Palmitate*
Zinc Aspartate	Zinc Glycinate	Zinc Phosphate
Zinc Carbonate	Zinc Hexametaphosphate*	Zinc Ricinoleate
Zinc Carbonate Hydroxide*	Zinc Hydroxide	Zinc Salicylate
Zinc Chloride	Zinc Lactate	Zinc Stearate
Zinc Chloride Hydroxide*	Zinc Laurate	Zinc Sulfate
Zinc Citrate	Zinc Myristate	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 CIR Science and Support Committee (CIR SSC) proposed that Zinc Oxide should be added to this report. The Panel did not find it appropriate to add this ingredient, stating that the bonds between zinc and oxygen bear considerable covalent character, and covalent bonding was the rationale for excluding another ingredient (i.e., Zinc Sulfide) from the report.

Noting that there are specific limits for zinc metal exposure via oral care products (resulting from these zinc salts), the Panel cautioned that zinc salts are rapidly absorbed from the gastrointestinal tract, and that zinc ingredients in oral care products would have high bioavailability. However, concern about systemic effects was mitigated by low use concentrations and by low toxicity of these ingredients in oral exposures.

In addition to identifying the concentration of zinc present in cosmetics via the zinc salts, the Panel determined that it was important to convert the doses of zinc salts administered in all toxicological studies to zinc equivalents. This conversion simplifies appropriate comparisons across all of the studies.

Mixed results were obtained in genotoxicity studies. The Panel determined, however, that the weight of the evidence indicated these ingredients are not genotoxic.

The Panel also noted epidemiology studies reporting an association between high levels of dietary zinc supplements and the incidence of prostate cancer. The authors of the studies acknowledged that they were unable to exclude effects of several confounding factors, and an association between excess (or high-level) zinc intake and prostate cancer remains unclear.

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

The Panel issued a final 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) Flower Water
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	Hamamelis Virginiana (Witch Hazel) Leaf Extract
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract*	Hamamelis Virginiana (Witch Hazel) Leaf Water
Hamamelis Virginiana (Witch Hazel) Extract	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 examined the oral toxicity, genotoxicity, carcinogenicity, dermal irritation, and sensitization studies of *Hamamelis virginiana* (witch hazel)-derived ingredients. However, because these ingredients are astringents and therefore may be irritating, and because these may be used in products applied near the eyes and mucous membranes, the Panel specified that products containing *Hamamelis virginiana* (witch hazel)-derived ingredients must be formulated to be non-irritating.

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

According to US FDA Voluntary Cosmetic Registration Program (VCRP) data received in 2018, Hamamelis Virginiana (Witch Hazel) Extract is reported to be used in 393 formulations (305 in leave-on formulations, 86 in rinse-off formulations, and 2 in formulations that are diluted for the bath). Hamamelis

Virginiana (Witch Hazel) Water is reported to be used in 376 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 125 or fewer formulations. Hamamelis Virginiana (Witch Hazel) Water has the highest reported maximum concentration of use, according to a survey performed by the Personal Care Products Council (Council); 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.

Tentative Safety Assessments

*Tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before **March 16, 2018**. 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 **June 4-5, 2018** meeting.*

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

The Panel issued a tentative report for public comment for the following 6 *Eucalyptus globulus*-derived ingredients with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

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

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

The Panel examined the data on oral, dermal and inhalation toxicity, ocular and dermal irritation, sensitization, reproduction, genotoxicity, and phototoxicity. The Panel also considered toxicity data on eucalyptol, a high concentration constituent of Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf/Twig Oil. The Panel noted the lack of toxicity and the lack of irritation and sensitization at relevant concentrations of these ingredients. The genotoxicity studies and the carcinogenicity study did not give cause for concern.

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

According to VCRP data received in 2018, Eucalyptus Globulus Leaf Oil is reported to be used in 433 formulations (214 leave-on formulations, 160 rinse-off formulations, and 59 formulations that are diluted for the bath). The results of the concentration of use surveys conducted by the Council in 2017 and 2018 indicate Eucalyptus Globulus Leaf Water is used at up to 1.4% in face and neck products; the rest of the ingredients with reported concentrations of use are used at a maximum of 1.2%.

***Ginkgo biloba*-Derived Ingredients**

The Panel issued a tentative report for public comment with the conclusion that the data are insufficient to determine the safety of the following 10 *Ginkgo biloba*-derived cosmetic ingredients:

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

**Not reported to be in current use.*

The data needed to issue a conclusion of safety for these cosmetic ingredients are:

- Method of manufacturing, composition, and impurities data for each of these ingredients, except Ginkgo Biloba Meristem Cell
- 28-Day dermal toxicity data for each of these ingredients.
  - Dependent on the results of these studies, additional data on other toxicological endpoints, such as developmental and reproductive toxicity and carcinogencity, may be needed
- Dermal irritation and sensitization data at leave-on use concentrations
- Ocular irritation data

The Panel considered the findings of the National Toxicology Program's (NTP's) carcinogenicity studies of a *Ginkgo biloba* leaf extract where positive carcinogenic effects were observed in animals, especially in the high dose groups. The *Ginkgo biloba* leaf extract evaluated by the NTP contained

unusually high concentrations of certain constituents that are markedly different from those found in the leaf extracts used in dietary supplements. The NTP study administered this specific leaf extract at high doses by gavage, allowing for concentrations in the blood that would not be achieved through cosmetic use. The leaf extract similar to that used in dietary supplements did not produce increased incidences of cancer in a dietary study. This, combined with a long history of use of *Ginkgo biloba* leaf extracts in folk medicine, indicate that the findings of the NTP's carcinogenicity study are not relevant to cosmetic use in humans.

Triphenyl Phosphate

The Panel issued a tentative report for public comment with the conclusion that Triphenyl Phosphate is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The Panel found that the systemic toxicity data, including developmental and reproductive toxicity and short-term toxicity studies, and dermal irritation and sensitization data in this report were sufficient. The Panel noted the lack of carcinogenicity data, but this gap was mitigated by multiple genotoxicity studies that were negative. This ingredient is only used in nail products and the maximum reported use concentration is 14.5%.

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* ***June 4-5, 2018*** *meeting.*

Polyfluorinated Polymers

The Panel issued an Insufficient Data Announcement (IDA) for the following 12 polyfluorinated polymer ingredients:

Fluoropolymers
- PTFE
- Hexafluoropropylene/Tetrafluoroethylene Copolymer

Fluorinated-Side-Chain Polymers
- Acrylates/Perfluorohexylethyl Methacrylate Copolymer
- Behenyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer
- C6-14 Perfluoroalkylethyl Acrylate/HEMA Copolymer
- Stearyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer

Fluorinated Polyethers
- Acrylates/Methoxy PEG-23 Methacrylate/Perfluorooctyl Ethyl Acrylate Copolymer
- PEG-10 Acrylate/Perfluorohexylethyl Acrylate Copolymer
- Polyperfluoroethoxymethoxy Difluoroethyl PEG Diisostearate
- Polyperfluoroethoxymethoxy Difluoroethyl PEG Ether
- Polyfluoroethoxymethoxy Difluorohydroxyethyl Ether
- Polyperfluoroethoxymethoxy Difluoromethyl Ether

The Panel determined that Polychlorotrifluoroethylene should be deleted from the group because the properties of this chemical are very different from the other polyfluorinated polymers under review. Furthermore, following a discussion relating to similarities and differences in chemistry within this ingredient group, the Panel determined that these ingredients should be sub-divided into fluoropolymers, fluorinated-side-chain polymers, and fluorinated polyethers, as indicated above.

These polyfluorinated polymers are reported to have the following functions in cosmetics: bulking agents, slip modifiers, film formers, viscosity increasing agents, dispersing agents, skin conditioning agents, skin protectants, and hair conditioning agents. Most of these ingredients reported to function as film formers in common. Additionally, these ingredients share in common an organic polymer backbone, wherein at least some of the carbon atoms in that backbone, or in side-chains, are perfluoronated.

According to 2017 VCRP data, PTFE is reported to be used in 377 cosmetic products (355 leave-on and 22 rinse-off products). The results of a concentration of a use survey conducted in 2017 by the Council indicate that PTFE is being used at concentrations up to 13% in leave-on products and at concentrations up to 2.4% in rinse-off products. Collectively, there are no indications that the remaining 10 polyfluorinated polymers are currently in use in cosmetic products in the US.

The Panel identified the following data needs:

- Method of manufacture and impurities data
- Skin sensitization data on PTFE at the highest maximum use concentration of 13%

Polyol Phosphates

The safety of the following 10 polyol phosphates is being evaluated in this safety assessment:

Sodium Phytate	Phytin	Xylityl Phosphate
Phytic Acid	Sodium Mannose Phosphate	Zinc Fructose Diphosphate
Disodium Glucose Phosphate	Trisodium Fructose Diphosphate	
Manganese Fructose Diphosphate	Trisodium Inositol Triphosphate	

Sodium Phytate, Phytic Acid, and Trisodium Inositol Triphosphate are reported to function as chelating agents in cosmetic products; Sodium Phytate and Phytic Acid are also reported to function as oral care agents; and Trisodium Fructose Diphosphate is reported to function as an antioxidant in cosmetic products. The remaining ingredients have the skin conditioning agent function in common, except for Xylityl Phosphate, which functions as a deodorant agent and exfoliant.

According to 2017 VCRP data, the greatest use frequency is reported for Sodium Phytate, which is reported to be used in 363 cosmetic products (225 of which are leave-on products). The results of a concentration of use survey conducted by the Council in 2016-2017 indicate that Phytic Acid is being used at concentrations up to 2% in leave-on products (body and hand products [not spray]), which is the greatest use concentration that is being reported for the polyol phosphates reviewed in this safety assessment.

The Panel issued an Insufficient Data Announcement with the following data requests on the polyol phosphates:

- Method of manufacture and impurities data on Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate
- Chemical characterization data on Xylityl Phosphate
- Absorption, distribution, metabolism, and excretion (ADME) data on Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate
- Skin sensitization data (animal or human) on Phytic Acid at the highest maximum use concentration of 2% or on a cosmetic product containing 2% Phytic Acid

The involvement of monosaccharides (i.e., glucose, fructose, mannose, and xylose) in redox reactions was considered by the Panel prior to determining the need for ADME data on the 6 sugar-phosphates (e.g., Trisodium *Fructose* Diphosphate).

146th Meeting Notes

Director's Report

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

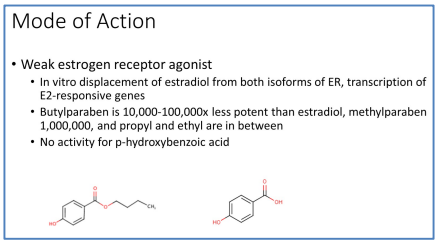
Dr. Heldreth thanked Dr. Daston for the cogent presentation made to the Panel at this meeting, and for the significant discussion involving issues associated with parabens and reproductive and developmental toxicity (or the lack thereof). He also reviewed CIR's accomplishments in 2017, including the completion of the safety assessment of 336 cosmetic ingredients and the publication of safety assessments covering 473 other ingredients in the peer-reviewed *International Journal of Toxicology*. Dr. Heldreth also welcomed the 3 new additions to the CIR staff: Alice Akinsulie, Priya Cherian, and Jinqiu Zhu.

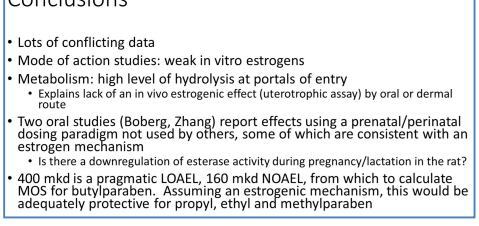
With regard to visibility of CIR, Dr. Heldreth mentioned the efforts to increase CIR participation with appropriate academies and agencies, including recent attendance by CIR staff at the 2018 meeting of the American Academy of Dermatology, Ms. Fiume's upcoming attendance at the national meeting of the Society of Toxicology, and an upcoming presentation by Dr. Heldreth at the Science Symposium of the German Cosmetic, Toiletry, Perfumery, and Detergent Association, in Frankfurt (Industrieverband Körperpflege- und Waschmittel e. V. (IKW); April 11th).

Presentation

The Panel requested further expert input on the topic of parabens and developmental and reproductive toxicity (DART). In response, Dr. George Daston, a Victor Mills Society Research Fellow at Proctor & Gamble, once again presented to the Panel on these ingredients. His briefing was titled, "Assessing the Developmental and Reproductive Toxicity of Parabens."

Dr. Daston acknowledged that there is a great deal of data on this subject that may at first seem quite conflicting. However, he stressed that much of these data 1) are irrelevant to the routes of exposure associated with intended cosmetic use, or otherwise did not account for the extensive metabolism of parabens to metabolites with no known DART activity; 2) are the result of poorly or uncommonly designed studies; 3) were not verified by other methods (as would traditionally be done); and/or 4) are not dose-dependent, and thereby likely erroneous. Indeed, Dr. Daston suggested, based on the relevant data, that a pragmatic no-observed-adverse-effect-level (NOAEL) of 160 mg/kg/day could be used to calculate a conservative margin of safety (MOS) for Butyl Paraben, and inferred to other members of the ingredient group.





Other Items:

Parabens

At the June 2017 meeting, the Panel agreed to re-open the parabens report, and added the relevant paraben salts and 4-Hydroxybenzoic Acid to the group. However, the Panel was concerned that new data from a developmental and reproductive toxicity (DART) study indicated reduced sperm counts and reduced expression of a specific enzyme, and a reduction in a specific cell marker in the testes of offspring of female rats orally dosed with 10 mg/kg/day Butylparaben during the gestation and lactation periods. Reductions in anogenital distance and other effects were reported at 100 mg/kg/day in this study. In comparison, the previous CIR safety assessment of the parabens included the calculation of margin of safety (MOS) values for adults and infants, assuming a no observed adverse effect level (NOAEL) of 1000 mg/kg/day from an older DART study. The Panel agreed that a subject matter expert should be consulted to review the reproductive toxicity data available for the parabens, and identify additional relevant data that the Panel should consider, if any. This expert should also provide professional opinions on the relevance of the animal-model toxicity endpoints reported in the DART studies available for assessing the safety of the parabens as used in cosmetics, and should evaluate the quality, and facilitate the interpretation of, the data on which NOAELs, lowest-observed adverse effect levels (LOAELs), and MOS values may be derived to assess the safety of these cosmetic ingredients. The Panel agreed to table the re-review of the parabens, at the June 2017 meeting, pending the input of such an expert.

Just such an expert, Dr. George Daston, presented on these very topics present at this CIR Expert Panel Meeting. Dr. Daston provided invaluable expertise, among other things, on the relevance of routes of exposure, paraben metabolism, and study design, in determining the validity of a multitude of reproductive and developmental studies for inclusion in this assessment. He also suggested the use of no observed adverse effect level (NOAEL) of 160 mg/kg/day to calculate a conservative margin of safety (MOS) for Butyl Paraben, which could then be inferred to other members of the parabens group.

Additional references were submitted by various stakeholders or discovered by CIR, many of which were provided for the Panel's consideration for inclusion in this report. The Panel reviewed the information presented at this meeting requested that all of this information, comprising not only the information from Dr. Daston's presentation, but also all of the submissions by various stakeholders, is incorporated into report before proceeding to the next stage.

Draft 2019 Priorities

Interested parties are invited to comment on the inclusion of the ingredients listed below as 2019 CIR Draft Priorities. The selection of these ingredients was based on those elected for cause, and those on the list of ingredients that have not yet been reviewed by the CIR Expert Panel that have the greatest number of uses reported to the VCRP in 2018. While the number of proposed new reports below is fewer than usual, a number of re-reviews and previously prioritized report projects are likely to be carried forward into 2019. Comments are also being sought on the additional ingredients that might be included in each ingredient family. Proposed ingredient families may be found starting at pdf page 25 in the document available at the following url, https://www.cir-safety.org/sites/default/files/admin_9.pdf. It is likely that not all of the ingredients listed below will be chosen for work in 2019. CIR plans to finalize the proposed 2019 Priority List at the June 2018 Panel meeting.

Per cause	***Frequency of Use (FOU)***
Benzisothiazolinone – potentially a new preservative	not reported in 2018 VCRP (6 uses in 2015)
Caprylhydroxamic Acid – *Contact Dermatitis* 77:159-162, 2017	147
Per FOU	
GLYCERYL ACRYLATE/ACRYLIC ACID COPOLYMER	383
SACCHARIDE ISOMERATE	365
PORTULACA OLERACEA (PURSLANE) EXTRACT	363
SODIUM LEVULINATE	331
GLUCONOLACTONE	329
ACETYL HEXAPEPTIDE-8	318
CHONDRUS CRISPUS (CARRAGEENAN) EXTRACT	299
ROSA DAMASCENA (DAMASK ROSE) FLOWER OIL	298
SALVIA OFFICINALIS (SAGE) LEAF EXTRACT	292
ROSA DAMASCENA (DAMASK ROSE) FLOWER WATER	289
DICAPRYLYL ETHER	288
PEG/PPG-8/3 DIISOSTEARATE	277
POLYQUATERNIUM-51	274
ACETYL GLUCOSAMINE	265
POLYQUATERNIUM-6	265
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	257

Acrylates Copolymer and Related Ingredients Re-Review Strategy

The Panel reviewed a strategy memo on the re-review of Acrylates Copolymer and Related Ingredients. This report was originally published in 2002. The Panel stated that it was appropriate to consolidate most of the related ingredients into this re-review. However, the Panel determined that Ethyl Methacrylate (not a polymer) and Glyceryl Polymethacrylate and Glyceryl Acrylate/Acrylic Acid Copolymer (to be reviewed in the near future as a family because of frequency of use of Glyceryl Polymethacrylate) would not be included. Additionally, Acrylates/VA Copolymer is being included in another report grouping, and will not be included in this re-review. Accordingly, the following ingredients comprise this family:

Acrylates copolymers and 33 related ingredients reviewed in 2002:

Acrylates/Ammonium Methacrylate Copolymer
Acrylates Copolymer
Acrylates/Hydroxyesters Acrylates Copolymer
Acrylates/Steareth-50 Acrylate Copolymer
Acrylates/Steareth-20 Methacrylate Copolymer
~~Acrylates/VA Copolymer~~
Ammonium Acrylates Copolymer
Ammonium Polyacrylate
Ammonium Styrene/Acrylates Copolymer
Ammonium VA/Acrylates Copolymer
AMP-Acrylates Copolymer
Ethylene/Acrylic Acid Copolymer
Ethylene/Acrylic Acid/VA Copolymer
Ethylene/Calcium Acrylate Copolymer
Ethylene/Magnesium Acrylate Copolymer
Ethylene/Methacrylate Copolymer
Ethylene/Sodium Acrylate Copolymer
Ethylene/Zinc Acrylate Copolymer
Lauryl Acrylate/VA Copolymer
Methacryloyl Ethyl Betaine/Acrylates Copolymer
Polyacrylic Acid
Potassium Aluminum Polyacrylate
Potassium Polyacrylate
Sodium Acrylate/Acrolein Copolymer
Sodium Acrylates Copolymer
Sodium Polyacrylate
Sodium Styrene/Acrylates Copolymer
Steareth-10 Allyl Ether/Acrylates Copolymer
Styrene/Acrylates Copolymer
Styrene/Acrylates/Ammonium Methacrylate Copolymer
VA/Butyl Maleate/Isobornyl Acrylate Copolymer
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer
VP/Dimethylaminoethylmethacrylate Copolymer

Previously un-reviewed ingredients

Acrylates/Beheneth-25 Methacrylate Copolymer
Acrylates/Beheneth-25 Methacrylate/Steareth-30 Methacrylate Copolymer
Acrylates/C5-8 Alkyl Acrylate Copolymer
Acrylates/C10-30 Alkyl Methacrylate Copolymer
Acrylates/C12-22 Alkyl Methacrylate Copolymer
Acrylates/Ceteareth-20 Methacrylate Crosspolymer
Acrylates/Ceteareth-20 Methacrylate Crosspolymer-2
Acrylates/Ceteth-20 Methacrylate Copolymer
Acrylates/C26-28 Olefin Copolymer
Acrylates Crosspolymer-3
Acrylates Crosspolymer-4
Acrylates Crosspolymer-5
Acrylates/Ethylhexyl Acrylate Copolymer
Acrylates/Hydroxyethyl Acrylate/Lauryl Acrylate Copolymer
Acrylates/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Acrylates/Laureth-25 Methacrylate Copolymer
Acrylates/Lauryl Methacrylate Copolymer
Acrylates/Lauryl Methacrylate/Tridecyl Methacrylate Crosspolymer
Acrylates/Methoxy PEG-4 Methacrylate Copolymer
Acrylates/Methoxy PEG-15 Methacrylate Copolymer
Acrylates/Methoxy PEG-23 Methacrylate Copolymer
Acrylates/Methoxy PEG-90 Methacrylate Crosspolymer
Acrylates/Palmeth-25 Acrylate Copolymer
Acrylates/Steareth-30 Methacrylate Copolymer
Acrylates/Stearyl Methacrylate Copolymer
Acrylates/VA Crosspolymer
Acrylic Acid/C12-22 Alkyl Acrylate Copolymer
Acrylic Acid/Stearyl Acrylate Copolymer
Ammonium Acrylates/Ethylhexyl Acrylate Copolymer
Ammonium Acrylates/Methyl Styrene/Styrene Copolymer
Ammonium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer
Behenyl Methacrylate/t-Butyl Methacrylate Copolymer
Butyl Acrylate/Cyclohexyl Methacrylate Copolymer
Butyl Acrylate/Ethylhexyl Methacrylate Copolymer
Butyl Acrylate/Hydroxyethyl Methacrylate Copolymer
Butyl Methacrylate/Acryoyloxy PG Methacrylate Copolymer
C12-22 Alkyl Acrylate/Hydroxyethylacrylate Copolymer
Cyclohexyl Methacrylate/Ethylhexyl Methacrylate Copolymer
Ethylhexyl Acrylate/Methoxy PEG-23 Methacrylate/Vinyl Acetate Copolymer
Ethylhexyl Acrylate/Methyl Methacrylate Copolymer
Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Lauryl Acrylate Crosspolymer
Lauryl Acrylate/VA Crosspolymer
Methoxy PEG-23 Methacrylate/Glyceryl Diisostearate Methacrylate Copolymer
Methyl Methacrylate/PEG/PPG-4/3 Methacrylate Crosspolymer
Polyacrylate-1 Crosspolymer

Poly C10-30 Alkyl Acrylate
Poly(Methoxy PEG-9 Methacrylate)
Polybutyl Acrylate
Polybutyl Methacrylate
Polyethylacrylate
Polyhydroxyethylmethacrylate
Polyisobutyl Methacrylate
Polymethyl Acrylate
Polypropyl Methacrylate
Polystearyl Methacrylate
Potassium Acrylate Crosspolymer
Potassium Acrylates Copolymer
Potassium Acrylates/Ethylhexyl Acrylate Copolymer
Sodium Acrylates/Beheneth-25 Methacrylate Crosspolymer
Sodium Acrylates/Ethylhexyl Acrylate Copolymer
Sodium Acrylate/Vinyl Alcohol Copolymer
Sodium Polymethacrylate

Crosslinked alkyl acrylates

Acrylates/C10-30Alkyl Acrylate Crosspolymer
Acrylates/C12-13 Alkyl Methacrylates/Methoxyethyl Acrylate Crosspolymer
Acrylates Crosspolymer
Acrylates/Ethylhexyl Acrylate Crosspolymer
Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer
Acrylates/PEG-4 Dimethacrylate Crosspolymer
Acrylates/Steareth-20 Methacrylate Crosspolymer
Acrylates/Vinyl Isodecanoate Crosspolymer
Acrylates/Vinyl Neodecanoate Crosspolymer
Allyl Methacrylate/Glycol Dimethacrylate Crosspolymer
Allyl Methacrylates Crosspolymer
Butyl Acrylate/Glycol Dimethacrylate Crosspolymer
C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer
Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer
Methacrylic Acid/PEG-6 Methacrylate/PEG-6 Dimethacrylate Crosspolymer
PEG/PPG-5/2 Methacrylate/Methacrylic Acid Crosspolymer
Potassium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Sodium Acrylates Crosspolymer-2
Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Sodium Acrylates/Vinyl Isodecanoate Crosspolymer
Stearyl/Lauryl Methacrylate Crosspolymer

Others

Polymethyl Methacrylate
Methyl Methacrylate Crosspolymer
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer
Carbomer

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.

- Acrylate/AcrylamideCcopolymers
- Alkoxylated Fatty Acmides
- Alkyl Lactyl Lactate Salts
- Benzyl Salicylate
- Brown Algae Ingredients
- Fatty Acids and Soaps
- Hydrogen Peroxide
- Hydroxyethyl Urea
- *Melaleuca alternifolia* (Tea Tree)-Derived Ingredients
- Organo-Titanium Ingredients
- Palm Tree-Derived Ingredients
- *Punica granatum* (Pomegranate)-Derived Ingredients
- Soy-Derived Ingredients
- *Triticum vulgare* (Wheat)-Derived Ingredients
- *Vanilla*-Derived Ingredients
- Vinylpyrrolidone Polymers
- Xanthine Alkaloids

Next CIR Expert Panel Meeting
Monday and Tuesday, June 4-5, 2018, at the Darcy Hotel, Washington, DC.
Please contact Carla Jackson (jacksonc@cir-safety.org) before the meeting if you plan to attend.