Post Meeting Announcement

Cosmetic Ingredient Review Expert Panel
151st Meeting (June 6-7, 2019) - Findings

June 12, 2019

- **Final Safety Assessments**
  - **Alkoxylated Fatty Amides – 40 ingredients – Safe with qualifications**
  - **Basic Red 76 – 1 ingredient – Safe as a hair dye**
  - **Alkanoyl Lactyl Lactates – 10 ingredients – Safe with qualifications**
  - **Polyaminopropyl Biguanide – 1 ingredient – Safe with qualifications, except insufficient for potentially inhaled products**

- **Tentative Safety Assessment**
  - **Parabens – 21 ingredients – Split conclusion (20 safe with qualifications; 1 insufficient)**
  - **Silica & Synthetic Silicates – Split conclusion (2 safe with qualifications; 22 insufficient)**

- **Insufficient Data Announcements**
  - **Glycerin Ethoxylates – 8 ingredients**
  - **MCI/MI – 2 ingredients (only when used together)**
  - **Caprylhydroxamic Acid – 1 ingredient**
  - **Soy-Derived Ingredients – 28 ingredients**
  - **Vanilla-Derived Ingredients – 9 ingredients**
  - **Capryloyl Salicylic Acid – 1 ingredient**

- **Re-Reviews**
  - **BHT – do not re-open**
  - **Imidazolidinyl Urea – do not re-open**
  - **EDTA – do not re-open**
  - **Acetyl Triethyl Citrates – do not re-open**

- **151st Meeting Notes**
  - **Director's Report**
  - **CIR 2020 Final Priorities**
  - **Re-Review Summary - Squalane & Squalene – 2 ingredients**
  - **Scientific Literature Reviews – under development**
  - **Next Expert Panel Meeting – Monday and Tuesday, September 16-17, 2019**

Final Safety Assessments

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 Unpublished data cited as references in CIR safety assessments are available for review.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

Alkoxylated Fatty Amides

The Panel issued a final report with the conclusion that the 40 ingredients named below are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

PEG-2 Cocamide	PEG-2 Lauramide*	PEG-15 Stearamide*
PEG-3 Cocamide	PEG-3 Lauramide	PEG-50 Stearamide*
PEG-4 Cocamide*	PEG-5 Lauramide*	PEG-5 Tallow Amide*
PEG-5 Cocamide	PEG-6 Lauramide	PEG-8 Tallow Amide*
PEG-6 Cocamide	PEG-11 Lauramide*	PEG-50 Tallow Amide
PEG-7 Cocamide*	PEG-3 Oleamide*	PEG-2 Tallowamide DEA*
PEG-11 Cocamide*	PEG-4 Oleamide*	Polyglyceryl-4-PEG-2 Cocamide*
PEG-20 Cocamide*	PEG-5 Oleamide*	PPG-2 Cocamide
PEG-3 Cocamide DEA*	PEG-6 Oleamide*	PPG-1 Hydroxyethyl Caprylamide*
PEG-20 Cocamide MEA*	PEG-7 Oleamide*	PPG-2 Hydroxyethyl Cocamide
PEG-6 Hydrogenated Palmamide*	PEG-9 Oleamide*	PPG-2 Hydroxyethyl Coco/Isostearamide
PEG-50 Hydrogenated Palmamide	PEG-4 Rapeseedamide	PPG-3 Hydroxyethyl Soyamide*
PEG-13 Hydrogenated Tallow Amide*	PEG-4 Stearamide*	
PEG-5 Lanolinamide*	PEG-10 Stearamide*	

**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 included in this family are structurally related as *N*-alkoxylated simple amides. The Panel determined that the information on the mono-*N*-alkoxyl-substituted ingredients informs the safety of the di-*N,N*-alkoxyl-substituted ingredients that are included in this report. Also, the Panel determined that the information on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide (which are the two ingredients with the highest reported frequency of use) could be read-across to other members of the group. The Panel remarked on the lack of carcinogenicity data; concerns for this lack of data, however, were mitigated by the sufficient, negative genotoxicity studies and the lack of structural alerts for carcinogenicity. Additionally, the margin of exposure (MOE) for PEG-4 Rapeseedamide (calculated by NICNAS) and PPG-2 Hydroxyethyl Cocamide (calculated by the CIR SSC) were acceptable; therefore, concerns regarding systemic toxicity following dermal exposure were mitigated.

There was a concern that the potential exists for dermal irritation with the use of products formulated using alkoxylated fatty amides. As a result, the Panel specified that products containing alkoxylated fatty amides must be formulated to be non-irritating.

The Panel also discussed the issues of impurities that could be of concern with this group of ingredients. The possible presence of 1,4-dioxane as an impurity is one concern, and the Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit this impurity in alkoxylated fatty amide ingredients before blending them into cosmetic formulations. Additionally, manufacturers should minimize primary amine impurities, and the Panel specified that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

Basic Red 76

The Panel issued a final report with the conclusion that Basic Red 76 is safe as a hair dye ingredient in the present practices of use and concentration described in the safety assessment. Basic Red 76 is currently reported to be used as a hair coloring agent (48 formulations), as well as a component in nail products (2 formulations). This ingredient is not an approved color additive by the US Food and Drug Administration (FDA), and thus use in a nail product is considered adulterated; however, hair dye use is exempt from such color additive regulations. The Panel recognized the use of this ingredient in nail products, but noted that evaluating the safety of this ingredient in formulations other than hair dye uses is outside of the Panel's purview. The results of the concentration of use survey conducted by the Council indicate that the highest concentration of use reported for Basic Red 76 is 0.35% in hair dyes and colors.

Alkanoyl Lactyl Lactate Salts

The Panel issued a final report with the conclusion that the 10 alkanoyl lactyl lactate 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 and non-sensitizing, which may be based on a QRA or other accepted methodologies.

Calcium Stearoyl Lactylate	Sodium Cocoyl Lactylate*	Sodium Oleoyl Lactylate*
Sodium Behenoyl Lactylate	Sodium Cupheoyl Lactylate*	Sodium Stearoyl Lactylate
Sodium Caproyl Lactylate	Sodium Isostearoyl Lactylate	
Sodium Caproyl/Lauroyl Lactylate	Sodium Lauroyl Lactylate	

**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.*

Alkyl lactyl lactate salts are the carboxylic acid salts of diesters that are formed between a fatty acid group and two equivalents of lactic acid. Acknowledging positive sensitization data on alkyl lactyl lactate salts, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application; thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies. The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using alkyl lactyl lactate salts. Thus, the Panel specified that products containing alkyl lactyl lactate salts must be formulated to be nonirritating.

Polyaminopropyl Biguanide

The Panel issued a final report with the conclusion that Polyaminopropyl Biguanide is 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, which may be based on a QRA or other accepted methodologies. However, the Panel also concluded that the data are insufficient to determine the safety of Polyaminopropyl Biguanide in products that may be inhaled. The Panel determined that the following data are needed to determine the safety of Polyaminopropyl Biguanide in products that may be inhaled:

- Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use. As part of this data insufficiency, use concentration data on this ingredient in aerosolized products and the particle size that is associated with the spray product are needed if Polyaminopropyl Biguanide is used in products that could be inhaled.

Due to concern over the skin sensitization potential of Polyaminopropyl Biguanide, the Panel previously requested the following data in addition to the above data request: 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 1000 µg/cm^2 (and recommendation to test at 500 µg/cm^2 as well). In response to this request, an HRIPT on 1% Polyaminopropyl Biguanide involving 108 subjects (Asian (~2%), biracial (~3%), Black (~ 23%), Caucasian (~ 33%), and Hispanic (~39%); Fitzpatrick skin types not stated) was provided. Polyaminopropyl Biguanide did not induce dermal sensitization in the subjects tested, and, using the results from this study, a QRA yielded a NESIL of 750 µg/cm^2. However, other data included in this CIR safety assessment indicate the potential for sensitization to Polyaminopropyl Biguanide, specifically in an LLNA, HRIPT, and in guinea pig maximization tests. Acknowledging the positive sensitization data on Polyaminopropyl Biguanide, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application and final formulation; thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies.

Tentative Safety Assessments

*Tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before **June 19, 2019**. Interested persons are given 60 days from the posting date (**August 18, 2019**) 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, but no later than August 18, 2019 for full consideration.** The updated reports may be scheduled for review by the CIR Expert Panel as early as at its **September 16-17, 2019** meeting.*

Silica & Synthetic Silicates

The Panel issued a tentative amended report for public comment with the conclusion that Silica and Hydrated Silica are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating. However, the Panel determined there were insufficient data to determine the safety of the remaining 22 ingredients listed below:

Aluminum Iron Calcium Magnesium Germanium Silicates*
Aluminum Iron Calcium Magnesium Zirconium Silicates*
Aluminum Iron Silicates*
Aluminum Silicate
Ammonium Silver Zinc Aluminum Silicate
Calcium Magnesium Silicate*
Calcium Silicate
Lithium Magnesium Silicate
Lithium Magnesium Sodium Silicate
Magnesium Aluminometasilicate
Magnesium Silicate
Magnesium Trisilicate
Potassium Silicate
Sodium Magnesium Aluminum Silicate*
Sodium Magnesium Silicate
Sodium Metasilicate
Sodium Potassium Aluminum Silicate
Sodium Silicate
Sodium Silver Aluminum Silicate*
Tromethamine Magnesium Aluminum Silicate*
Zinc Silicate*
Zirconium Silicate*

Ingredients in red were previously reviewed by the Panel.

**Not reported to be in use.*

The Panel emphasized that this report reviews the safety of synthetic amorphous Silica and synthetic amorphous silicate ingredients. Crystalline silica is not toxicologically similar to amorphous silica and would need to be reviewed separately.

The Panel reviewed the current safety test data on amorphous Silica and Hydrated Silica and determined that these two ingredients do not pose an inhalation safety risk. The exposures that were tested in inhalation studies were at much higher concentrations than those possible with cosmetic use, and had very few adverse effects. The carcinogenicity study used such high concentrations of Silica that the noted effects on the lymph nodes were due to the overload of the animal system: incidental inhalation of Silica in cosmetics is not a concern.

The data on the remaining ingredients were considered insufficient to determine the conclusion on safety. The additional data needed for the 22 silicate ingredients comprise:

- Chemical characterization (structure), composition, and impurities data for the silicate ingredients
- Method of manufacturing and/or source data for the silicate ingredients
  - Depending on the information provided, additional data on toxicological endpoints may be needed

Parabens

The Panel issued a revised tentative amended report for public comment with the conclusion that the following 20 alkyl parabens are safe in the present practices of use and concentration described in the safety assessment when the sum of paraben concentrations in final formulation does not exceed 0.8%.

Butylparaben
Calcium Paraben*
Ethylparaben
Isobutylparaben
Isopropylparaben
Methylparaben
Potassium Butylparaben*
Potassium Ethylparaben*
Potassium Methylparaben*
Potassium Paraben*
Potassium Propylparaben*
Propylparaben
Sodium Butylparaben
Sodium Ethylparaben
Sodium Isobutylparaben
Sodium Isopropylparaben*
Sodium Methylparaben
Sodium Paraben
Sodium Propylparaben
4-Hydroxybenzoic Acid*

**Not reported to be in current use.*

However, the Panel concluded that the available data are insufficient to determine the safety of Benzylparaben. (This ingredient is not reported to be in use.) The data needed to determine the safety of this ingredient comprise a no-observed-adverse-effect-level (NOAEL) derived from developmental and reproductive toxicity (DART) studies.

The Panel evaluated the recently discovered additional biomonitoring and epidemiological papers on these ingredients. The Panel also requested the incorporation of subcutaneous studies into the report, and an explanation of the lack of relevance of this route of administration to cosmetic exposure.

Because of the extensive metabolism of parabens, the Panel determined that safety data for one of these alkyl parabens can be used to support the safety of the other alkyl parabens.

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, but no later than August 11, 2019 for full consideration****. These reports may be scheduled for review by the CIR Expert Panel as soon as the* ***September 16-17, 2019*** *meeting.*

Caprylhydroxamic Acid

The Panel reviewed the safety of Caprylhydroxamic Acid for the first time and issued an insufficient data announcement (IDA). Several human repeated insult patch tests (HRIPTs) were included in the draft report, that described testing at various concentrations of Caprylhydroxamic Acid. Although the test results are largely negative, there were some alerts for sensitization in HRIPTs on formulations containing less than the maximum reported use concentration of Caprylhydroxamic Acid. Because the potential for sensitization could not be ruled out completely based on the reactions observed in the HRIPTs, combined with reactions reported in patients following the use of Caprylhydroxamic Acid in a reformulated moisturizer in Finland, and the absence of a local lymph node assay or guinea pig maximization test to demonstrate a lack of sensitization potential, the following data were requested:

- Human repeated insult patch test at maximum use concentrations
  - a minimum of 100 subjects, preferably with Fitzpatrick skin types 1 - 4
  - based on these results, a QRA should be performed, and a no-expected-sensitization-induction-level (NESIL) should be determined

The Panel noted that Caprylhydroxamic Acid penetrates the skin. However, the negative results reported in a 13-week oral repeated dose toxicity study, an oral developmental and reproductive study, and in vitro genotoxicity studies included in the report, mitigated concerns about systemic toxicity.

Hydroxamates, as a class, are chelating agents, and some are capable of the inhibition of a variety of enzymes, including ureases, peroxidases, and matrix metalloproteinases. However, based on the structure of Caprylhydroxamic Acid, it is not expected to be an effective inhibitor; none of the effective inhibitors contain a straight alkyl chain.

Additionally, the Panel also noted that nitrosamide formation is theoretically possible. However, they also noted that such formation is highly unlikely with Caprylhydroxamic Acid.

Capryloyl Salicylic Acid

The Panel issued an IDA with the following data requests on Capryloyl Salicylic Acid:

- Impurities
- Phototoxicity

The CIR Expert Panel published a safety assessment of Salicylic Acid and 16 salicylates in 2003. That safety assessment included Capryloyl Salicylic Acid, which was included in the grouping because, at the time, it was mischaracterized and defined as an ester. However, it is now known that this ingredient is a ketone. This is the first time the Panel has reviewed this ingredient as a ketone.

According to the *Dictionary*, Capryloyl Salicylic Acid is reported to function as a skin conditioning agent. Capryloyl Salicylic Acid is used in 104 cosmetic products (93 leave-on and 11 rinse-off). This ingredient is used at concentrations up to 0.5% (in moisturizing products, not spray), the highest reported maximum use concentration for leave-on formulations. In rinse-off products, Capryloyl Salicylic Acid is used at concentrations up to 0.4% (in paste masks and mud packs).

The Panel discussed the issue of skin sensitization potential for this ingredient. Capryloyl Salicylic Acid induced skin sensitization in guinea pig maximization tests at challenge concentrations of 0.5%, 2%, and 5%, but not at 1%. However, in HRIPTs, cosmetic products containing 0.5% or 2% Capryloyl Salicylic Acid were classified as non-sensitizing. After reviewing the HRIPT results and considering that the highest reported maximum use concentration of Capryloyl Salicylic Acid is 0.5% in leave-on cosmetic products, the Panel was reassured that the sensitization potential of exposure to this ingredient via cosmetic use is not a risk.

Glycerin Ethoxylates

The Panel issued an IDA for the following 8 glycerin ethoxylates ingredients:

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

The Panel reviewed the safety of these glycerin ethoxylates for the first time, and found the data were insufficient to determine safety. The results of a concentration of use survey conducted by the Council in 2018 indicate that Glycereth-26 is used at up to 1% in body and hand spray formulations which may result in incidental inhalation exposure. The Panel discussed the issue of incidental inhalation exposure from aerosol spray moisturizers, and body and hand products. The Panel also asked to see data from similar alkoxylated ingredients for potential inference.

In order to determine the safety on these ingredients, the following data were requested:

- Impurities
- Method of manufacture
- Inhalation toxicity data

Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI)

The Panel issued an IDA for the cosmetic use of the ingredient mixture, MCI/MI. (This report was initiated as a re-review.) The Panel requested an inhalation study of at least 3 months in duration that is in accordance with the Organization for Economic Co-operation and Development (OECD) test guideline (TG) 413. This request is in response to reports of adverse events observed in infants following inhalation exposure to humidifier disinfectants that contained this preservative mixture.

The Panel noted the results of a QRA for skin sensitization performed by the CIR Science and Support Committee. The results indicated that some leave-on products with MCI/MI, at the recommended safe concentration of 7.5 ppm, may increase the risk of sensitization induction. In most rinse-off products, 15 ppm MCI/MI was not associated with a potential increased risk of skin sensitization induction. Regarding safety of topical (non-inhalable products), the Panel found that MCI/MI should be formulated to be non-sensitizing in dermal applications based on the results of a QRA or other similar methodologies. The Panel cautioned that following these recommendations may not necessarily prevent the elicitation of allergic reactions in individuals who are already allergic to MCI/MI. Individuals previously sensitized to MCI/MI should avoid products that contain this ingredient mixture, or either constituent.

Soy-Derived Ingredients

The Panel issued an IDA for the following 28 soy-derived ingredients:

Glycine Max (Soybean) Callus Culture
Glycine Max (Soybean) Callus Culture Extract
Glycine Max (Soybean) Callus Extract
Glycine Max (Soybean) Fiber
Glycine Max (Soybean) Flower/Leaf/Stem Juice
Glycine Max (Soybean) Leaf Cell Extract
Glycine Max (Soybean) Leaf Extract
Glycine Max (Soybean) Phytoplacenta Conditioned Media
Glycine Max (Soybean) Phytoplacenta Extract
Glycine Max (Soybean) Pulp
Glycine Max (Soybean) Seed Extract
Glycine Max (Soybean) Seedcake Extract
Glycine Max (Soybean) Seedcoat Extract
Glycine Max (Soybean) Seed Powder
Glycine Max (Soybean) Sprout Extract
Glycine Soja (Soybean) Extract
Glycine Soja (Soybean) Fiber
Glycine Soja (Soybean) Flour
Glycine Soja (Soybean) Germ Extract
Glycine Soja (Soybean) Hull
Glycine Soja (Soybean) Lipids
Glycine Soja (Soybean) Phytoplacenta Extract
Glycine Soja (Soybean) Seed
Glycine Soja (Soybean) Seedcake Extract
Glycine Soja (Soybean) Seed Extract
Glycine Soja (Soybean) Seed Powder
Glycine Soja (Soybean) Seed Water
Glycine Soja (Soybean) Sprout Extract

The Panel noted the lack of genotoxicity and carcinogenicity data, but considered the lack of those data to be mitigated as these ingredients are commonly ingested as food and food products, and exposure via oral ingestion would be much higher than exposure from cosmetics. The much greater exposure via food and food products, and the lack of adverse events resulting therefrom, also mitigated the concern for possible estrogenic effects. In addition, the Panel noted an occupational exposure study in which workers displayed asthmatic symptoms after inhalation exposure to soy. The Panel attributed the respiratory symptoms therein to the prolonged duration of exposure, which would not be a relevant issue with cosmetic use. Tyrosinase inhibition was apparent in a study involving Glycine Soja (Soybean) Sprout Extract; however, the Panel decided that this was not of concern as this was an in vitro study and the doses used in this study were much higher than what would be used in cosmetics. The possible tumor-promoting effects of soy were evaluated and were mitigated, as persistent activation of certain pathways would need to occur before tumor promotion could be a concern.

However, in order to make a conclusion of safety on these ingredients, the Panel requested sensitization data on Glycine Soja (Soybean) Seed Extract at the current maximum use concentration of 2%. In addition, the Panel requested data identifying the composition, method of manufacture, or general characteristics of the callus ingredients.

Vanilla-Derived Ingredients

The Panel issued an IDA for the following 9 vanilla-derived ingredients, from *Vanilla planifolia* and *Vanilla tahitensis* plants:

Vanilla Planifolia Fruit Extract
Vanilla Planifolia Flower Extract
Vanilla Planifolia Fruit Oil
Vanilla Planifolia Fruit Water
Vanilla Planifolia Leaf Cell Extract
Vanilla Planifolia Seed
Vanilla Planifolia Seed Powder
Vanilla Tahitensis Fruit Extract
Vanilla Tahitensis Seed

The Panel issued the following data requests on Vanilla Planifolia Flower Extract:

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

Vanilla tahitensis is mainly cultivated in French Polynesia but is also found, together with *Vanilla planifo*lia, in New Guinea (Papua New Guinea and Indonesia). According to another source, *Vanilla tahitensis* samples from Papua New Guinea and *Vanilla planifolia* samples from Madagascar (Bourbon vanilla) are among the vanilla samples that are commercially available. Botanicals, such as *Vanilla planifolia* and *tahitensis*-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects under certain conditions.

According to 2019 VCRP data, Vanilla Planifolia Fruit Extract is reported to be used in 370 cosmetic products (232 leave-on products, 133 rinse-off products, and 5 products that are diluted for (bath) use). Of the vanilla-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency of use.

The results of a concentration of use survey conducted by the Council in 2017 indicate that Vanilla Planifolia Fruit Extract is used at maximum concentrations of up to 0.33% in leave-on products (face and neck products) and maximum use concentrations up to 0.25% in rinse-off products (skin cleansing products). These are the highest use concentrations in leave-on and rinse-off products reported for the vanilla-derived ingredients that are reviewed in this safety assessment.

Re-Reviews

Acetyl Trialkyl Citrates

At the December 1999 Panel meeting, the Panel concluded that Acetyl Triethyl Citrate, Acetyl Tributyl Citrate, Acetyl Trihexyl Citrate, and Acetyl Trioctyl Citrate (now known as Acetyl Triethylhexyl Citrate) are safe as used in cosmetic formulations, and issued a final report. The final report was published in 2002. Because it has been at least 15 years since this report was published, in accordance with CIR Procedures, the Panel again considered whether the safety assessment of these 4 ingredients should be reopened. After considering new studies and updated use data on these 4 ingredients, the Panel determined to not re-open the safety assessment.

After reviewing assays involving cell models with reporter genes (i.e., in vitro cell reporter assays), the Panel noted that Acetyl Tributyl Citrate and Acetyl Triethyl Citrate may produce adaptive effects or trigger activation of reporter constructs. However, the Panel stated that toxicity cannot be concluded unless the effect is evaluated in vivo. In other words, these assay results are not evidence of a toxic effect, and the results would have to be validated in vivo to determine whether or not the effect observed is actually a toxic effect.

Acetyl Tributyl Citrate is being used in leave-on products at concentrations up to 8.9% (7% in the original report), and the frequency of use of this ingredient has increased significantly since the initial review of this ingredient group. Acetyl Triethyl Citrate is reportedly used in rinse-off and leave-on products, but current use concentration data were not reported. Acetyl Trihexyl Citrate and Acetyl Triethylhexyl Citrate are not reported to be in current use.

BHT

The Panel first published a review of the safety of BHT (Butylated Hydroxytoluene) in 2002, concluding that, "BHT is safe as used in cosmetic formulation," as described in that report. Because it has been at least 15 years since the report was published, in accordance with CIR Procedures, the Panel considered whether the safety assessment of BHT should be re-opened.

The Panel reviewed data that have been published since the last review, as well as updated frequency and concentration of use data. The frequency of use has increased significantly. The available studies, along with the case literature, demonstrate no significant irritation or sensitization. Recognizing the low concentration at which this ingredient is currently used in cosmetic formulations and the lack of case reports in spite of the increased use, the Panel reaffirmed the original conclusion, and determined to not re-open the safety assessment.

EDTA & Salts

The Panel first published a review of the safety of EDTA and its corresponding salts in 2002. The Panel concluded that EDTA, Calcium Disodium EDTA, Diammonium EDTA, Dipotassium EDTA, TEA-EDTA, Tetrasodium EDTA, Tripotassium EDTA, Trisodium EDTA, HEDTA, and Trisodium HEDTA are safe as used in cosmetic formulations. Because it has been at least 15 years since the publishing of this report, in accordance with CIR Procedures, the Panel considered whether the safety assessment of EDTA and its corresponding salts should be re-opened.

The Panel reviewed the data that have been published since the last report, as well as the updated frequency and concentration of use data. The frequency of use of several of these ingredients increased significantly. The Panel noted the potential for phototoxicity from a study involving protoporphyrin, but concerns were mitigated as the concentrations of EDTA used in that study were extremely high. In addition, the Panel noted the lack of genotoxicity and clinical effects in studies involving these ingredients. Therefore, the Panel reaffirmed the original conclusion, and determined to not re-open the safety assessment.

Imidazolidinyl Urea

The CIR Expert Panel first reviewed the safety of Imidazolidinyl Urea in 1980, concluding that this ingredient was "safe when incorporated in cosmetic products in amounts similar to those presently marketed." In 2001, after considering new studies and updated use data on this ingredient, the Panel determined to not re-open the safety assessment. Because it has been at least 15 years since the first re-review summary was published, in accordance with CIR Procedures, the Panel again considered whether the safety assessment of Imidazolidinyl Urea should be re-opened.

The Panel reviewed data that have been published since the last re-review, as well as updated frequency and concentration of use data. The frequency of use has decreased significantly. The Panel noted that Imidazolidinyl Urea is a formaldehyde-releasing preservative and use of these types of ingredients as a whole has decreased. The Panel determined that there were no new relevant data that would inform a new review of this ingredient. Therefore, the Panel reaffirmed the original conclusion, and determined to not re-open the safety assessment.

151st Meeting Notes

Director's Report

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the Cosmetic Ingredient Review program. He also reported on a status change for 12 ingredient conclusions. In 2017, the Panel issued a final report on the Safety Assessment of Citrus Plant- and Seed-Derived Ingredients as Used in Cosmetics. The Panel reviewed the available data presented and concluded that 18 of these ingredients are safe in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing. However, the data for the remaining 12 ingredients were insufficient to determine safety. Since the 2-year clock has expired, those 5 ingredients reported to be in use at the time are thus moved to the "use not supported category" and those 7 with no reported uses now fall under the "zero use" categorization.

Citrus Aurantifolia (Lime) Oil
Citrus Aurantium (Bitter Orange) Oil
Citrus Aurantium Dulcis (Orange) Oil
Citrus Aurantium Sinensis Powder
Citrus Limon (Lemon) Flower/Leaf/Stem Extract
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder*
Citrus Grandis (Grapefruit)*
Citrus Iyo Oil*
Citrus Limon (Lemon) Flower/Leaf/Stem Oil*
Citrus Limon (Lemon) Leaf/Peel/Stem Oil*
Citrus Nobilis (Mandarin Orange) Water*
Citrus Unshiu Extract*

**Not reported to be in current use.*

Final 2020 Priorities

The CIR Procedures require preparation of the Draft 2020 Priority List for public comment by June 1, 2019. The Draft 2020 Priority List was issued for public comment earlier (March 2019) in the process to allow more time for the acquisition of data. Comments at the April 2019 Expert Panel meeting were considered and incorporated, where appropriate, into a Draft Final 2020 Priority List. Comments at the June 2019 Expert Panel meeting, on that Draft Final version, were considered and incorporated here, in this Final 2020 Priority List. The list is based on stakeholder requests; frequency of use data (FOU) from FDA's Voluntary Cosmetic Registration Program (VCRP), received from the FDA on February 13, 2019; and on CIR staff and Panel workflow. The Final Priorities for 2020 are essentially the same as those finalized for 2019; however, this list has been updated with 2019 frequency of use data, a report in progress (Caprylhydroxamic Acid) has been removed from the list because it is already under review, an ingredient (Benzisothiazolinone) was removed for zero FOU, and an ingredient (Calcium Sulfate) was removed for significantly declining FOU (between years 2018 and 2019). Additionally, three items were suggested for incorporation in this list. However, each was deferred to future prioritization, in order to gather more information.

While this Final Priority list below includes only the lead ingredients, groupings are provided for each in the final document (https://www.cir-safety.org/sites/default/files/CIR_Final_2020_Priorities.pdf) There are 23 reports covering 185 ingredients on the Final 2020 Priorities List. Reports previously prioritized and on the CIR docket at the end of 2019, as well as a number of re-reviews of previous assessments, will supplement the total number of ingredients to be assessed in 2020. Interested parties are encouraged to submit pertinent data to the CIR, as soon as possible, for use in the development of the Scientific Literature Reviews for these ingredients.

Final 2020 Priorities List

Ingredients	*Frequency of Use (FOU)*
For cause	
BASIC BROWN 17 – a hair dye	51
Per FOU	
HONEY	1002
SACCHARUM OFFICINARIUM (SUGARCANE) EXTRACT	447
EQUISETUM ARVENSE EXTRACT	338
SACCHARIDE ISOMERATE	455
PORTULACA OLERACEA (PURSLANE) EXTRACT	481
UBIQUINONE	374
DIATOMACEOUS EARTH	213
SODIUM LEVULINATE	390
GLUCONOLACTONE	369
ACETYL HEXAPEPTIDE-8	379
HONEY EXTRACT	359
CHONDRUS CRISPUS EXTRACT	350
ROSA DAMASCENA FLOWER OIL	328
SALVIA OFFICINALIS (SAGE) LEAF EXTRACT	325
ROSA DAMASCENA FLOWER WATER	331
DICAPRYLYL ETHER	344
PEG/PPG-8/3 DIISOSTEARATE	290
POLYQUATERNIUM-51	310
DIACETONE ALCOHOL	223
ACETYL GLUCOSAMINE	276
POLYQUATERNIUM-6	280
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	279

Re-Review Summary

Squalane and Squalene

The Panel approved the re-review summary of Squalane and Squalene, reaffirming that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration. This conclusion was originally published by CIR in 1982. Limited new data that were identified in the published literature, as well as updated information regarding frequencies of use, provided by the FDA, and maximum use concentrations of use, provided by the Council, were reviewed by the Panel.

Scientific Literature Reviews

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

- Acrylate/Acrylamide Copolymers
- Adenosine Ingredients
- Amino Acid Diacetates
- Ascorbyl Glucoside
- Basic Brown 17
- *Carica papaya* (Papaya)-Derived Ingredients
- *Cocos nucifera* (Coconut)-Derived Ingredients
- Honey-Derived Ingredients
- *Hordeum vulgare*-Derived Ingredients
- *Melaleuca alternifolia* (Tea Tree)-Derived Ingredients
- Polysilicone-11
- Saccharide Humectants
- *Scutellaria baicalensis*-Derived Ingredients
- Tris(Tetramethylhydroxypeperidinol) Citrate
- Wheat-Derived Ingredients

Next CIR Expert Panel Meeting

Monday and Tuesday, September 16-17, 2019 at the Westin DC City Center Hotel, Washington, DC.
Please contact Carla Jackson (jacksonc@cir-safety.org) before the meeting if you plan to attend.