Announcement

Cosmetic Ingredient Review Expert Panel
140th Meeting (September 26-27, 2016) - Findings

September 30, 2016

- Final Safety Assessments
  - Citrus Peel-Derived Ingredients – 47 ingredients
  - Fatty Acyl Sarcosines and Their Salts – 14 ingredients
  - Helianthus annuus (Sunflower)-Derived Ingredients – 12 ingredients
  - Phosphoric Acid and Its Salts – 31 ingredients
  - Polyglyceryl Fatty Acid Esters – 274 ingredients
  - Trimellitic Anhydride Copolymers – 6 ingredients

- Tentative Safety Assessments
  - Acryloyldimethyltaurate Polymers – 21 ingredients
  - Butyrospermum parkii (Shea)-Derived Ingredients – 13 ingredients
  - Citrus Flower- and Leaf-Derived Ingredients – 33 ingredients
  - Citrus Plant- and Seed-Derived Ingredients – 32 ingredients
  - Etidronic Acid and Its Salts – 4 ingredients
  - Hydrofluorocarbon 152a – 1 ingredient
  - Rosa canina-Derived Ingredients – 12 ingredients

- Re-Review - none

- Insufficient Data Announcement
  - Alkane Diols – 10 ingredients
  - Humulus lupulus (Hops)-Derived Ingredients – 6 ingredients

- 140th Meeting Notes
  - Director’s Report
    - Presentation on in vitro Skin Sensitization Test Methods
  - Scientific Literature Reviews posted on the CIR website
  - Scientific Literature Reviews under development
  - Next Expert Panel Meeting – Monday and Tuesday, December 5-6, 2016
Final Safety Assessments

Final safety assessments and final amended 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 Unpublished data cited as references in CIR safety assessments are available for review.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 or final amended safety assessment is incorrect may petition the CIR Expert Panel to amend the safety assessment.

Citrus Peel-Derived Ingredients

The Panel issued a final report with the conclusion that the following 47 Citrus peel-derived ingredients are safe as used in the present practices of use and concentration when formulated to be non-sensitizing and non-irritating, provided that leave-on products do not contain more than 0.0015% (15 ppm) 5-methoxypsoralen (5-MOP).

Citrus Aurantifolia (Lime) Peel*  Citrus Junos Peel Extract
Citrus Aurantifolia (Lime) Peel Extract  Citrus Junos Peel Powder
Citrus Aurantifolia (Lime) Peel Powder  Citrus Limon (Lemon) Peel Water*
Citrus Aurantifolia (Lime) Peel Water*  Citrus Limon (Lemon) Peel
Citrus Aurantium Amara (Bitter Orange) Peel  Citrus Limon (Lemon) Peel Water*
Citrus Aurantium Amara (Bitter Orange) Peel Extract  Citrus Limon (Lemon) Peel Powder
Citrus Aurantium Amara (Bitter Orange) Peel Powder  Citrus Limon (Lemon) Peel Water*
Citrus Aurantium Bergamia (Bergamot) Peel Water  Citrus Limon (Lemon) Peel Waxes
Citrus Aurantium Dulcis (Orange) Peel Extract  Citrus Natsudaidai Peel Extract*
Citrus Aurantium Dulcis (Orange) Peel Powder  Citrus Nobilis (Mandarin Orange) Peel Water*
Citrus Aurantium Dulcis (Orange) Peel Wax  Citrus Nobilis (Mandarin Orange) Peel Powder*
Citrus Aurantium Sinensis Peel Extract*  Citrus Paradisi (Grapefruit) Peel Extract
Citrus Aurantium Tachibana Peel Extract  Citrus Reticulata (Tangerine) Peel Extract
Citrus Depressa Peel Extract  Citrus Reticulata (Tangerine) Peel Powder*
Citrus Depressa Peel Powder*  Citrus Shunkokan Peel Extract*
Citrus Grandis (Grapefruit) Peel*  Citrus Sukiki Peel Extract*
Citrus Grandis (Grapefruit) Peel Extract  Citrus Tachibana/Reticulata Peel Powder*
Citrus Grandis (Grapefruit) Peel Powder*  Citrus Tangelo Peel Powder*
Citrus Hassaku/Natsudaidai Peel Powder*  Citrus Tangerina (Tangerine) Peel*
Citrus Iyo Peel Extract*  Citrus Tangerina (Tangerine) Peel Extract
Citrus Iyo Peel Water*  Citrus Unshiu Peel Extract
Citrus Jabara Peel Extract  Citrus Unshiu Peel Powder
Citrus Jabara Peel Powder*  Citrus Unshiu Peel Water*
Citrus Jabara Peel 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 available dermal irritation and sensitization data supported the safety of these Citrus peel-derived ingredients. However, these ingredients have the potential to cause phototoxicity. The Panel determined that the International Fragrance Association (IFRA) standard for the quantity of 5-MOP that may be present in these ingredients is adequate to prevent 5-MOP-induced phototoxicity.

The Panel acknowledged that multiple botanical ingredients combined in one formulation, may each contribute to the final concentration of a single constituent of concern. When formulating products containing Citrus peel-derived ingredients, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects.

Fatty Acyl Sarcosines and Their Salts

The Panel issued a final amended report with the conclusion that the following 10 previously reviewed fatty acyl sarcosines and salts, as well as 4 additional salts that have not been previously reviewed, are safe as used in the present practices of use and concentration when formulated to be non-irritating; these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed:

Previously Reviewed
Cocoyl Sarcosine  Ammonium Cocoyl Sarcosinate*
Lauroyl Sarcosine  Ammonium Lauroyl Sarcosinate
Myristoyl Sarcosine  Sodium Cocoyl Sarcosinate
Oleoyl Sarcosine  Sodium Lauroyl Sarcosinate
Stearoyl Sarcosine  Sodium Myristoyl Sarcosinate

Additional Salts
Potassium Cocoyl Sarcosinate*  Sodium Oleoyl Sarcosinate*
Potassium Lauroyl Sarcosinate*  Sodium Palmitoyl Sarcosinate

* Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.
The Panel’s conclusion supersedes the original conclusion issued for the 10 previously reviewed ingredients. The original conclusion that was published in 2001 specified a concentration limit for use in leave-on products, and stated that the data were insufficient to determine safety in products that are likely to be inhaled. The Panel removed the concentration limit because concentration of use data, which were not included in the 2001 report, are now available, and sensitization data are available from studies conducted at the highest concentration reported to be used. Data are also available to address concerns about incidental inhalation.

*Helianthus annuus* (Sunflower)-Derived Ingredients

The Panel issued a final report with the conclusion that the following 9 *Helianthus annuus* (sunflower)-derived ingredients are safe as used in the present practices of use and concentration as described in this safety assessment:

- Helianthus Annuus (Sunflower) Seed Extract
- Helianthus Annuus (Sunflower) Flower Extract
- Helianthus Annuus (Sunflower) Seed
- Helianthus Annuus (Sunflower) Seed Butter*
- Helianthus Annuus (Sunflower) Seedcake
- Helianthus Annuus (Sunflower) Seed Flour*
- Helianthus Annuus (Sunflower) Seed Wax
- Hydrogenated Sunflower Seed Extract*
- Hydrolyzed Sunflower Seed Wax

The Panel concluded that the available data are insufficient for evaluating the safety of the following 3 *Helianthus annuus* (sunflower)-derived ingredients in cosmetic products:

- Helianthus Annuus (Sunflower) Extract
- Helianthus Annuus (Sunflower) Leaf/Stem Extract*
- Helianthus Annuus (Sunflower) Sprout Extract*

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

The additional data needed include:

- Method of manufacture
- Composition of these ingredients, especially protein content (including 2S albumin)
- Impurities

The Panel discussed the potential for albumins of the 2S protein fraction of sunflower seeds to cause IgE-mediated-immediate (Type I) hypersensitivity reactions. The incidence of persons with sensitivity to *Helianthus annuus* (Sunflower)-derived ingredients is low, and the Panel noted that reactions attributable to contact with products containing such ingredients not been observed in their clinical experience. The Panel agreed with Dr. Stefano Luccioli, Senior Medical Advisor at the Food and Drug Administration’s (FDA) Office of Food Additive Safety (OFAS), who indicated that a warning label for seed or tree nut allergic individuals would not be warranted, but labelling cosmetic products as containing *Helianthus annuus* (sunflower) seed-derived ingredients would likely satisfy any pertinent condition of safety for these ingredients. However, the Panel emphasized that persons with sensitivity to 2S albumins from seeds, nuts or legumes should be cautious when using formulations that contain *Helianthus annuus* (Sunflower)-derived ingredients.

The Expert Panel expressed concern about pesticide residues, heavy metals, and substances from plants of other species (weeds) that may be present in botanical ingredients. To address these concerns, the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

**Phosphoric Acid and Its Salts**

The Panel issued a final report with the conclusion that the following 31 ingredients are safe as used in the present practices of use and concentration as described in this safety assessment, when formulated to be non-irritating:

- Phosphoric Acid
- Ammonium Phosphate
- Dicalcium Phosphate
- Calcium Dihydrogen Phosphate
- Calcium Phosphate
- Calcium Potassium Sodium Phosphate*
- Calcium Pyrophosphate
- Diammonium Phosphate
- Dicalcium Phosphate Dihydrate
- Dipotassium Phosphate
- Disodium Phosphate
- Disodium Pyrophosphate
- Magnesium Hydrogen Phosphate*
- Magnesium Phosphate*
- Metaphosphoric Acid*
- Pentapotassium Triphosphate
- Pentasodium Triphosphate*
- Phosphate Buffered Saline*
- Potassium Metaphosphate
- Potassium Phosphate
- Sodium Hexametaphosphate
- Sodium Metaphosphate
- Sodium Polyphosphate*
- Sodium Trimetaphosphate*
- Tetrapotassium Pyrophosphate
- Tricalcium Phosphate
- Trisodium Phosphate
- Trimagnesium Phosphate
Trisodium Phosphate

*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 the broad range of results for irritation reported for Phosphoric Acid or its salts at concentrations within and outside of the range of those used in cosmetic products. The Panel discussed reports suggesting that Potassium Phosphate can cause renal damage, and may be associated with renal cancer. They stated that the high doses of Potassium Phosphate used in the studies most probably promoted tumors through irritation. Furthermore, there is a large number of negative genotoxicity studies, and human and animal studies that indicate Potassium Phosphate exposures are not strongly associated with renal damage or renal cancers.

The greatest reported use frequency is for Phosphoric Acid (489 formulations, mostly rinse-off), followed by Dicalcium Phosphate (327 formulations, mostly leave-on). Dicalcium Phosphate Dihydrate has the highest maximum concentration of use; it is used at concentrations up to 49% in rinse-off products (dentifrices).

**Polyglyceryl Fatty Acid Esters**

The Panel issued a final report with the conclusion that the following 274 polyglyceryl fatty acid esters are safe as used in the present practices of use and concentration when formulated to be non-irritating:

| Adansonia Digitata Seed Oil Polyglyceryl-6 Esters* | Polyglyceryl-2 Palmitate* |
| Almond Oil/Polyglyceryl-10 Esters* | Polyglyceryl-2 Sesquicaprylate* |
| Apricot Kernel Oil Polyglyceryl-3 Esters* | Polyglyceryl-2 Sesquiosostearate |
| Apricot Kernel Oil Polyglyceryl-4 Esters* | Polyglyceryl-2 Sesquioleate* |
| Apricot Kernel Oil Polyglyceryl-5 Esters* | Polyglyceryl-2 Sesquistearate |
| Apricot Kernel Oil Polyglyceryl-6 Esters* | Polyglyceryl-2 Stearate |
| Apricot Kernel Oil Polyglyceryl-10 Esters* | Polyglyceryl-2 Tetrahydroxystearate/Macadamiate/Sebacate* |
| Argan Oil Polyglyceryl-6 Esters* | Polyglyceryl-2 Tetraisostearate |
| Astrocarum Vulgare Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Caprylate |
| Avocado Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Cocoaate* |
| Babassu Oil Polyglyceryl-4 Esters | Polyglyceryl-3 Dicaprate* |
| Babassu Oil Polyglyceryl-6 Esters | Polyglyceryl-3 Disteareate/Stearate |
| Bertholletia Excelsa Seed Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Hydroxystearate |
| Borage Seed Oil Polyglyceryl-4 Esters* | Polyglyceryl-3 Isostearate |
| Borage Seed Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Isostearate/Laurate |
| Candelilla/Jojoba/Rice Bran Polyglyceryl-3 Esters | Polyglyceryl-3 Isostearate/Laurate |
| Caprylic/Capric Glycerides Polyglyceryl-10 Esters | Polyglyceryl-3 Isostearate/Laurate |
| Carapa Guianensis Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Isostearate/Laurate |
| Castor Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Isostearate/Stearate |
| Cocoa Butter Polyglyceryl-6 Esters* | Polyglyceryl-3 Myristate* |
| Coconut Oil Polyglyceryl-6 Esters | Polyglyceryl-3 Oleate |
| Coffee Seed Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Palmitate |
| Diisostearoyl Polyglyceryl-3 Dimer Dilinoleate | Polyglyceryl-3 Pentacaprylate/Caprate* |
| Glyceryl/Polyglyceryl-6 Isostearate/Behenate Esters | Polyglyceryl-3 Pentaoleate |
| Hazelnut Seed Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Pentaricinoleate |
| Linseed Oil Polyglyceryl-4 Esters* | Polyglyceryl-3 Pentaricinoleate |
| Macadamia Seed Oil Polyglyceryl 6 Esters* | Polyglyceryl-3 Pentaricinoleate |
| Macadamia Seed Oil Polyglyceryl 6 Esters Behenate | Polyglyceryl-3 Pentaricinoleate |
| Mauritia Flexuosa Seed Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Pentaricinoleate |
| Olive Oil Polyglyceryl-3 Esters* | Polyglyceryl-3 Polyglyceryl-3 Rice Branate* |
| Olive Oil Polyglyceryl-4 Esters* | Polyglyceryl-3 Ricinoleate |
| Olive Oil Polyglyceryl-6 Esters* | Polyglyceryl-3 Soyaate/Shea Butterate* |
| Palm Kernel Oil Polyglyceryl-4 Esters* | Polyglyceryl-3 Stearate |
| Palm Oil Polyglyceryl-3 Esters* | Polyglyceryl-3 Stearate SE* |
| Palm Oil Polyglyceryl-4 Esters | Polyglyceryl-3 Triisostearate* |
| Palm Oil Polyglyceryl-5 Esters* | Polyglyceryl-3 Triolivate* |
| Palm Oil Polyglyceryl-6 Esters* | Polyglyceryl-4 Almondate/Shea Butterate* |
| Parinari Curatellifolia Oil Polyglyceryl-6 Esters* | Polyglyceryl-4 Caprate |
| Pinus Sibirica Seed Oil Polyglyceryl-6 Esters* | Polyglyceryl-4 Caprylate |
| Polyglyceryl-12 Caprylate* | Polyglyceryl-4 Caprylate/Caprate* |
| Polyglyceryl-12 Diisostearate | Polyglyceryl-4 Cocoaate |
| Polyglyceryl-12 Disteareate | Polyglyceryl-4 Dilaurate* |
| Polyglyceryl-12 Isopalmitate | Polyglyceryl-4 Disteareate* |
| Polyglyceryl-12 Isopalmitate/Sebacate* | Polyglyceryl-4 Hazelnutseedate* |
| Polyglyceryl-12 Isostearate | Polyglyceryl-4 Isostearate |
| Polyglyceryl-12 Laurate | Polyglyceryl-4 Isostearate/Laurate* |
| Polyglyceryl-12 Myristate* | Polyglyceryl-4 Laurate |
| Polyglyceryl-12 Oleate | Polyglyceryl-4 Laurate/Sebacate* |
In April, the Panel issued a tentative conclusion that the data were insufficient to determine safety for any type of cosmetic use for all 6 trimellitic anhydride copolymers. Since that meeting, method of manufacture and composition data were received for Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer. The Panel's final conclusion supersedes the tentative conclusion issued in April.

The Panel discussed the penetration enhancement properties of some of these ingredients, and noted that these ingredients are extensively metabolized to yield common nutrients and physiological intermediates. Also, the extensive negative irritation and sensitization data and the concentration of use data indicate that these ingredients are safe as used under the conditions described in the safety assessment.

**Trimellitic Anhydride Copolymers**

The Panel issued a final report with the conclusion that Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer and Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer are safe as used in the present practices of use and concentration in nail product formulations, but the data are insufficient to determine that the following 4 trimellitic copolymers, which are not reported to be in use, are safe for use in cosmetic formulation:

- Acrylamide/Sodium Acryloyldimethyltaurate/ Acrylic Acid Copolymer
- Acrylamide/Sodium Acryloyldimethyltaurate
- Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer
- Propylene Glycol/Sebacic Acid/Trimellitic Anhydride

The additional data needed to evaluate the safety of these ingredients for use in nail products are:

- Method of manufacture; and
- Composition data.

In addition, the following data are needed to evaluate the safety of these ingredients for uses other than in nail products:

- Molecular weight,
- Impurities, specifically, the amount of residual monomer in each copolymer
- Metabolism, specifically, whether these ingredients are metabolized in the skin;
- Dermal absorption; if absorbed, then genotoxicity and reproductive toxicity data are needed; and
- Dermal irritation and sensitization at maximum leave-on concentration of use.

In April, the Panel issued a tentative conclusion that the data were insufficient to determine safety for any type of cosmetic use for all 6 trimellitic anhydride copolymers. Since that meeting, method of manufacture and composition data were received for Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer, and an Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) determined Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer is a polymer of low concern (PLC) and is not considered to pose an unreasonable risk to public health of workers and the public when used as a component of cosmetic nail products.

The Panel’s final conclusion supersedes the tentative conclusion issued in April.

**Tentative Safety Assessments**

Tentative and revised tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before October 7, 2016. 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 and no later than November 11, 2016. The updated reports may be scheduled for review by the CIR Expert Panel at its December 5-6, 2016 meeting.

**Acryloyldimethyltaurate Polymers**

The Panel issued a tentative report for public comment with the conclusion that the following 21 acryloyldimethyltaurate polymers are safe as used in the present practices of use and concentration:

- Acrylamide/Sodium Acryloyldimethyltaurate Copolymer
- Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Esters</th>
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<tbody>
<tr>
<td>Safflower Seed Oil Polyglyceryl-6 Esters*</td>
<td>Sunflower Seed Oil Polyglyceryl-5 Esters*</td>
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<tr>
<td>Schinziophyton Rautanenii Kernel Oil Polyglyceryl-6 Esters*</td>
<td>Sunflower Seed Oil Polyglyceryl 6 Esters*</td>
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<td>Sclerocarya Birrea Seed Oil Polyglyceryl-6 Esters*</td>
<td>Sunflower Seed Oil Polyglyceryl 10 Esters*</td>
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<tr>
<td>Sclerocarya Birrea Seed Oil Polyglyceryl-10 Esters*</td>
<td>Sweet Almond Oil Polyglyceryl-4 Esters*</td>
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<tr>
<td>Sesame Oil Polyglyceryl-6 Esters*</td>
<td>Sweet Almond Oil Polyglyceryl-6 Esters*</td>
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<tr>
<td>Shea Butter Polyglyceryl-3 Esters*</td>
<td>Trichilia Emetica Seed Oil Polyglyceryl-6 Esters*</td>
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<td>Shea Butter Polyglyceryl-4 Esters*</td>
<td>Trischotearyl Polyglyceryl-3 Dimer Dilinoleate</td>
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<td>Shea Butter Polyglyceryl-6 Esters*</td>
<td>Watermelon Seed Oil Polyglyceryl-6 Esters *</td>
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<td>Soybean Oil Polyglyceryl-6 Esters*</td>
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<tr>
<td>Sunflower Seed Oil Polyglyceryl 3 Esters*</td>
<td>Ximenia Americana Seed Oil Polyglyceryl-6 Esters*</td>
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<tr>
<td>Sunflower Seed Oil Polyglyceryl-4 Esters*</td>
<td>Sunflower Seed Oil Polyglyceryl-5 Esters*</td>
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*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.

These ingredients are esterification products of polyglycerin chains and fatty acids that vary in numbers of glycerin and fatty-acid equivalents and lengths of the fatty acids.

In addition, the following data are needed to evaluate the safety of these ingredients for uses other than in nail products:

- Method of manufacture;
- Composition data.

In addition, the following data are needed to evaluate the safety of these ingredients for uses other than in nail products:

- Molecular weight;
- Impurities, specifically, the amount of residual monomer in each copolymer;
- Metabolism, specifically, whether these ingredients are metabolized in the skin;
- Dermal absorption; if absorbed, then genotoxicity and reproductive toxicity data are needed; and
- Dermal irritation and sensitization at maximum leave-on concentration of use.

In April, the Panel issued a tentative conclusion that the data were insufficient to determine safety for any type of cosmetic use for all 6 trimellitic anhydride copolymers. Since that meeting, method of manufacture and composition data were received for Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer, and an Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) determined Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer is a polymer of low concern (PLC) and is not considered to pose an unreasonable risk to public health of workers and the public when used as a component of cosmetic nail products.
Ammonium Acryloyldimethyltaurate/Beheneth-25 Methacrylate Crosspolymer
Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer
Ammonium Acryloyldimethyltaurate/Laureth-7 Methacrylate Copolymer
Ammonium Acryloyldimethyltaurate/Steareth-25 Methacrylate Crosspolymer*
Ammonium Acryloyldimethyltaurate/Steareth-8 Methacrylate Copolymer
Ammonium Acryloyldimethyltaurate/Vinyl Formamide Copolymer*
Ammonium Acryloyldimethyltaurate/VP Copolymer
Ammonium Polyacryloyldimethyl Taurate
Dimethylacrylamide/Sodium Acryloyldimethyltaurate Crosspolymer
HEA/Sodium Acryloyldimethyltaurate/Steareth-20 Methacrylate Copolymer
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Crosspolymer
Sodium Acrylate/Acryloyldimethyltaurate/Steareth-20 Methacrylate Copolymer
Sodium Acrylate/Sodium Acryloyldimethyl Taurate/VP Copolymer
Sodium Acryloyl Dimethyl Taurate/PEG-8 Diacrylate Crosspolymer*
Sodium Acryloyldimethyltaurate/Methacrylamidolauric Acid Copolymer
Sodium Acryloyldimethyltaurate/VP Crosspolymer
Sodium Polyacryloyldimethyl Taurate

* 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 the group.

The Panel noted that these are large molecules and that dermal penetration would be unlikely to occur. The Panel advised that formulators should use current good manufacturing practices (cGMPs) to ensure that residual monomers (i.e., vinyl formamide and methacrylamidolauric acid) are minimized in these ingredients and the final products. The Panel noted that the presence of acrylamide is limited to 5 ppm in cosmetic formulations containing Polyacrylamide and that this limit was also appropriate for the acryloyldimethyltaurate polymers.

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

The Panel issued a tentative report for public comment with the conclusion that the following 9 ingredients are safe as used in the present practices of use and concentration as described in this safety assessment:

- Butyrospermum Parkii (Shea) Butter
- Hydrogenated Shea Oil*
- Butyrospermum Parkii (Shea) Oil
- Shea Butter Glyceride
- Butyrospermum Parkii (Shea) Butter Extract
- Shea Butter Glycerides
- Butyrospermum Parkii (Shea) Butter Unsaponifiables
- Shea Oleine
- Hydrogenated Shea Butter

The Panel concluded that the data on the 4 ingredients listed below are insufficient to determine safety.

- Butyrospermum Parkii (Shea) Nut Extract
- Butyrospermum Parkii (Shea) Nut Shell Powder
- Butyrospermum Parkii (Shea) Seedcake Extract
- Hydrolyzed Shea Seedcake Extract*

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

The additional data needed to evaluate the safety of these 4 ingredients are:

- Method of manufacturing
- Composition and impurities data
- Sensitization data

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

The ingredient Butyrospermum Parkii (Shea) Butter is reported to be used at concentrations up to 100%. While there are no safety test data for this ingredient at this maximum concentration, the Panel was not concerned about dermal irritation or sensitization because of clinical experience and the absence of adverse event reports.

**Citrus Flower- and Leaf-Derived Ingredients**

The Panel issued a revised tentative report for public comment with the conclusion that the following 33 ingredients are safe as used in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing.

- Citrus Aurantifolia (Lime) Flower Extract
- Citrus Aurantium Amara (Bitter Orange) Flower Extract
- Citrus Aurantifolia (Lime) Leaf Oil*
- Citrus Aurantium Amara (Bitter Orange) Flower Oil
Citrus Aurantium Amara (Bitter Orange) Flower Water
Citrus Aurantium Amara (Bitter Orange) Flower Wax
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract*
Citrus Aurantium Bergamia (Bergamot) Leaf Extract
Citrus Aurantium Bergamia (Bergamot) Leaf Oil
Citrus Aurantium Dulcis (Orange) Flower Extract
Citrus Aurantium Dulcis (Orange) Flower Oil
Citrus Aurantium Dulcis (Orange) Flower Wax
Citrus Aurantium Dulcis (Orange) Flower
Citrus Aurantium Dulcis (Orange) Leaf Extract
Citrus Clementina Leaf Cell Extract*
Citrus Depressa Flower Water*
Citrus Grandis (Grapefruit) Leaf Extract*
Citrus Hystrix Leaf Extract*
Citrus Hystrix Leaf Oil

*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.

Multiple botanical ingredients in one formulation may each contribute to the final concentration of a single constituent. When formulating products containing Citrus flower- and leaf-derived ingredients, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. Constituents of concern found in some of these ingredients include limonene and linalool, the hydroperoxides of which are skin sensitizers. The International Fragrance Association (IFRA) limit for these peroxides is 20 mmol/L.

**Citrus** Plant- and Seed-Derived Ingredients

The Panel issued a revised tentative report for public comment with the conclusion that the following 13 ingredients are safe as used in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing.

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract*
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil
Citrus Aurantium Dulcis (Orange) Seed Extract
Citrus Australasica Seed Oil*
Citrus Depressa Seed Oil*
Citrus Glauca Seed Oil*
Citrus Grandis (Grapefruit) Oil
Citrus Grandis (Grapefruit) Seed Extract
Citrus Grandis (Grapefruit) Seed Oil
Citrus Grandis Peel/Seed Extract*

The Panel concluded that the data on 19 ingredients listed below are insufficient to determine safety.

Citrus Aurantiumol (Lime) Oil
Citrus Aurantium (Bitter Orange) Oil
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder*
Citrus Aurantium Dulcis (Orange) Oil
Citrus Aurantium Sinensis Powder
Citrus Grandis (Grapefruit)*
Citrus Grandis (Grapefruit) Extract
Citrus Iyo Oil*
Citrus Jabara Péricarp Extract*
Citrus Junos Extract

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

The data needed to evaluate the safety of these 19 ingredients are:

- Method of manufacturing
- Chemical composition and impurities
- Irritation and sensitization data
- If the composition data for these Citrus plant- and seed-derived ingredients are substantially different from that of the Citrus peel-, flower-, and leaf-derived ingredients, then systemic toxicity studies such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity studies are needed, as well as UV absorption spectra

Multiple botanical ingredients, in one formulation, may each contribute to the final concentration of a single constituent. When formulating products containing Citrus plant- and seed-derived ingredients, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects.

**Etidronic Acid and Its Salts**

The Panel issued a tentative report for public comment with the conclusion that the following 4 ingredients are safe as used in the present practices of use and concentration as described in this safety assessment.
Etidronic Acid
Disodium Etidronate
Tetrapotassium Etidronate
Tetrasodium Etidronate

The Panel acknowledged the moderately widespread clinical use of these ingredients to treat bone diseases and determined that there were no systemic concerns about their use in cosmetics based on the data presented. Although there were no phototoxicity or photosensitization data, the Panel agreed that these ingredients are not expected to absorb UV light. Inhalation data on sodium etidronate and genotoxicity data on sodium etidronate and trisodium etidronate were used to address concerns about the lack of inhalation toxicity data and the minimal genotoxicity data available for the ingredients in this safety assessment.

Etidronic Acid was reported to have the greatest number of uses (341) in cosmetic formulations. Etidronic Acid also had the highest reported maximum concentration of use (0.9% in other hair coloring preparations) in rinse-off products and the highest maximum concentration of use (0.12% in other fragrance preparations) reported in leave-on products.

Hydrofluorocarbon 152a

The Panel issued a tentative report for public comment with the conclusion that Hydrofluorocarbon 152a is safe as used in the present practices of use and concentration.

This ingredient is a gas that functions as a propellant and is used at concentrations up to 80% in hair sprays and 35% in underarm deodorants. Hydrofluorocarbon 152a is largely inert, is rapidly volatilized and dispersed in ambient air upon application, and, when inhaled, is rapidly cleared from the body in exhaled air. The Panel found the overall safety profile of this ingredient to be favorable and concluded that it was safe for use in cosmetics.

Rosa canina-Derived Ingredients

The Panel issued a tentative report for public comment with the conclusion that the following 12 Rosa canina-derived ingredients are safe as used in the present practices of use and concentration in cosmetics as described in this safety assessment when formulated to be non-irritating and non-sensitizing:

- Rosa Canina Fruit Extract
- Rosa Canina Bud Extract
- Rosa Canina Flower
- Rosa Canina Flower Extract
- Rosa Canina Flower Powder
- Rosa Canina Flower Oil
- Rosa Canina Fruit
- Rosa Canina Fruit Juice
- Rosa Canina Leaf Extract
- Rosa Canina Seed
- Rosa Canina Seed Extract
- Rosa Canina Seed Powder

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

The inhibition of skin pigmentation by Rosa Canina Fruit Extract was reported in in vitro and in vivo studies. The Panel discussed the potential of quercetin and proanthocyanidins to cause skin depigmentation. However, the Panel noted that the use concentrations of this ingredient and, thus, the levels of these components in cosmetics, are below the threshold of concern for this effect.

The Panel observed that linalool and eugenol, which are components of Rosa canina-derived ingredients, are constituents of concern because of the potential for their hydroperoxides to induce sensitization. The IFRA has established a limit for the peroxides of these 2 components, which should not be exceeded. The Panel noted that because final product formulations may contain multiple botanical ingredients, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. The Panel expressed concern about pesticide residues, heavy metals, and substances from plants of other species (weeds) that may be present in botanical ingredients. To address these concerns, the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

Insufficient Data Announcement

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 by November 11, 2016. These reports may be scheduled for review by the CIR Expert Panel at its December 5-6, 2016 meeting.

Alkane Diols

The Panel issued an insufficient data announcement for the following 10 ingredients:

- Propanediol
- 1,4-Butanediol
- 1,5-Pentanediol
- Hexanediol
- Octanediol
1,10-Decanediol
Methylpropanediol
2,3-Butanediol
Butyl Ethyl Propanediol
Isopentylidol

The additional data needed included:

- Method of manufacturing data for all ingredients
- Impurities data for all ingredients, particularly indicating whether or not 2,5-Hexanediol is an impurity of Hexanediol (i.e., 1,6-Hexanediol)
- Additional Penetration Enhancement data for all ingredients
- Neurotoxicity data for Isopentylidol
- Concentration of use data for 1,4-Butanediol

**Humulus lupulus** (hops)-derived ingredients

The Panel issued an Insufficient Data Announcement for the following 6 **Humulus lupulus** (hops)-derived ingredients:

- Humulus Lupulus (Hops) Extract
- Humulus Lupulus (Hops) Cone Extract
- Humulus Lupulus (Hops) Cone Oil
- Humulus Lupulus (Hops) Flower Extract
- Humulus Lupulus (Hops) Strobile
- Humulus Lupulus (Hops) Stem Extract*

The data needs are:

- Composition and sensitization for Humulus Lupulus (Hops) Extract at maximum concentration of use (0.6%)
- Composition for Humulus Lupulus (Hops) Stem Extract.

The Panel noted the presence of β-myrcene at 25.4% in Humulus Lupulus (Hops) Cone Oil. This constituent is a potential irritant, and there is a National Toxicology Program study showing increased incidences of kidney tumors in male rats and liver tumors in male mice after oral administration of 1.0 g/kg/day β-myrcene for 2 years. The Panel noted that the increased incidence of kidney tumors in this study is likely attributable to a mechanism that is not relevant to humans, and the increased incidence of liver tumors is attributable to the high background incidence and susceptibility to the development of liver tumors that is characteristic of the mouse strain used in the study, and is also not predictive of carcinogenicity in humans. Further, the dosage rates of β-myrcene administered orally to the rats and mice in the study were much greater than any reasonable worst-case exposure to β-myrcene that could occur from hops-derived ingredients in cosmetics. However, concerns about β-myrcene, and possibly other constituents, cannot be addressed fully by the Panel, because the available information is not sufficient to characterize adequately the compositions of hops-derived cosmetic ingredients. The Panel emphasized the importance, generally, of adequately characterizing the compositions of cosmetic ingredients derived from plants, as manufactured and supplied to formulators of cosmetic products.

**140th Meeting Notes**

**Director’s Report**

Dr. Gill seconded Dr. Bergfeld’s comments on the wonderful dinner and celebration for the 40th Anniversary of CIR. Mr. Peter Hutt, who was instrumental in founding and developing the organization, gave a brief history of CIR, complemented the organization for its impressive work to date and challenged the Panel and staff to continue building on the current successes. Family, friends and colleagues including past Director of CIR, Dr. Alan Andersen, attended the celebration held in Georgetown.

Dr. Gill mentioned Dr. Bergfeld’s participation in a hearing before the Senate Health, Education, Labor, and Pension Committee on September 22, 2016. She provided the Committee with information on the work of the CIR Expert Panel.

At the June 2016 meeting, the Panel requested a presentation on an *in chemico* skin sensitization test method named the Direct Peptide Reactivity Assay (DPRA). The results of a DPRA were summarized in the safety assessment of *Butyrospermum parkii* (shea)-Derived Ingredients. The DPRA was noted as a method recently validated by the European Centre for the Validation of Alternative Methods (ECVAM) and the subject of the Organisation of Economic Co-operation and Development (OECD) Test Guideline (TG 442C). In response to the Panel’s request, Dr. Donald Bjerke presented a briefing titled “Skin Sensitization: In Vitro Methods and Risk Assessment.” Dr. Gill, and the Panel, expressed the CIR’s appreciation to Dr. Donald Bjerke’s for his informative presentation. Dr. Bjerke is a toxicologist, Principal Scientist at the Procter & Gamble Company, and member of the CIR Science and Support Committee (CIR SSC).

Lastly, Dr. Gill reminded the meeting participants that the next meeting is scheduled for December 5-6. She encouraged all who have data to submit for safety assessments that were reviewed at this meeting and those that are scheduled to be discussed at the December 2016 meeting, to provide that data as soon as possible.

**Presentation on *in vitro* Skin Sensitization Test Methods.**

Dr. Donald Bjerke summarized the evolution of skin-sensitization testing methods, beginning with the development of *in vivo* methods, including the guinea pig tests *circa* 1970 and the Local Lymph Node Assay (LLNA) in the 1990s, followed by more recent efforts to develop alternatives to whole animal tests. The latter include *in silico*, *in vitro*, and *in chemico* approaches, such as computational modeling of molecular interactions, tests of dendritic-
cell gene activation, and peptide reactivity assays, respectively. He also stated that there are several computational tools available to predict the dermal penetration and metabolism of haptons and hapten precursors, the small electrophilic molecules that cause skin sensitization after penetrating the stratum corneum of the skin. In fact, the mechanism of skin sensitization is well characterized and represented by a well-defined Adverse Outcome Pathway (AOP) that describes sensitization as a series of key chemical and biological events.

Dr. Bjerke noted three non-animal test methods that have been developed to differentiate sensitizers from non-sensitizers based on the ability of chemicals to react with skin proteins. These methods include the DPRA and the Peroxidase Peptide Reactivity Assay (PPRA), which are both in chemico assays, and a cell-based assay that signals the covalent binding of the hapten to cellular proteins through the expression of luciferase-gene constructs. He also mentioned other in vitro assays that reflect subsequent key events along the AOP. Of these assays, 3 have been scientifically validated and have achieved regulatory acceptance, including the DPRA, and 5 are under assessment for validation by the ECVAM.

Dr. Bjerke used the slide shown to illustrate, conceptually, that the results of in chemico protein reactivity assays (like the DPRA), in silico predictions, and in vitro assays that represent, in aggregate, multiple key events of the AOP, can be integrated to estimate the potencies of chemicals identified as sensitizers. He emphasized that the ultimate goal of these efforts is to develop integrated testing strategies (ITSs) that directly predict the risk of skin sensitization in human beings, rather than the likelihood of positive results in LLNAs.

Dr. Bjerke also discussed some of the limitations of the DPRA, in particular. For example, the DPRA depends on the ability of a hapten to react with the cysteine and lysine residues of proteins. Thus, the DPRA cannot be used to identify haptens that react preferentially with other amino acids. Further, the DPRA cannot be used to identify pro-haptens, and the extent to which the DPRA can be used to identify pre-haptens is not clear. Research is ongoing to advance the development of the DPRA to address these limitations.

The slides for this presentation are available at http://www.cir-safety.org/sites/default/files/CIREP_092616_DL_Bjerke.pdf

Scientific Literature Reviews

- These literature reviews are currently posted on the CIR website at http://www.cir-safety.org/ingredients/glossary/all

  Ethers of Ascorbate
  Hydroxy-3,4-Methylenedioxyaniline
  Monoalkylglycol Dialkyl Acid Esters
  Plant-Derived Proteins & Peptides

  Draft reports for these ingredient families, along with any unpublished data submitted by interested parties, may be presented to the Panel at its meeting on December 5-6, 2016.

- These literature reviews are currently under development and may be announced during the first half of 2017.

  Alkoxylated Fatty Amides
  Brown Algae ingredients
  Ethers, Ester, & Salts Panthenol and Pantothenic Acid
  Fatty Acids and Soaps (Linoleic Acid, etc.)
  Ginkgo biloba-Derived Ingredients
  Melaleuca alternifolia (Tea Tree)-Derived Ingredients
  Milk-Derived Proteins & Peptides
  Skin-Derived Proteins & Peptides

Next CIR Expert Panel Meeting

Monday and Tuesday, December 5-6, 2016, at The Melrose Georgetown Hotel, Washington, DC 20037 --- Please contact Carla Jackson (jacksonc@cir-safety.org) before the meeting if you plan to attend.