Announcement

Cosmetic Ingredient Review Expert Panel
141st Meeting (December 5-6, 2016) - Findings

December 9, 2016

- Final Safety Assessments
  - Acid Violet 43 – 1 ingredient
  - Alkoxyl Alkyl Silanes – 4 ingredients
  - Carbonate Salts – 6 ingredients
  - *Citrus* Flower- and Leaf-Derived Ingredients – 33 ingredients
  - *Citrus* Plant- and Seed-Derived Ingredients – 30 ingredients
  - Dialkyl Carbonates – 6 ingredients
  - PEG Propylene Glycol Derivatives – 7 ingredients
  - Saccharide Esters – 40 ingredients

- Tentative Safety Assessments
  - Butyl Polyoxyalkylene Ethers – 46 ingredients
  - Ethers and Esters of Ascorbic Acid – 7 ingredients
  - Hydroxy-3,4-Methylenedioxyaniline HCl – 1 ingredient

- Re-Review - none

- Insufficient Data Announcement
  - Monoalkylglycol Dialkyl Acid Esters – 28 ingredients
  - Persulfates – 3 ingredients
  - Plant-Derived Proteins and Peptides – 19 ingredients

- 141st Meeting Notes
  - Director’s Report
    - Presentation on Endocrine Activity
  - Scientific Literature Reviews posted on the CIR website
  - Scientific Literature Reviews under development
  - Next Expert Panel Meeting – Monday and Tuesday, April 10-11, 2017
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 Unpublished data cited as references in CIR safety assessments are available for review.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.

Acid Violet 43

The Panel issued a final amended report with the conclusion that Acid Violet 43 is safe in the present practices of use and concentration for use in hair dye formulations. This supersedes the conclusion published in the original assessment on this ingredient published in 2001.

In the original report, safety test data on the certified color Ext. D&C Violet No. 2 (which has the same chemical structure as Acid Violet 43) were used to evaluate the safety of Acid Violet 43 because there were no data available for Acid Violet 43. Therefore, the conclusion for Acid Violet 43 included impurity specifications for the certified color. In 2013, the European Commission Scientific Committee on Consumer Safety issued an opinion on Acid Violet 43 that included test data on both Acid Violet 43 and Ext. D&C Violet No. 2. The Panel determined that the new information was sufficient to assess the safety of Acid Violet 43 and removed the impurity specifications for the certified color from the conclusion.

Alkoxyl Alkyl Silanes

The CIR Panel issued a final report with the conclusion that the following 4 alkoxyl alkyl silanes are safe as used in the present practices of use and concentration:

- Bis-Stearoxydimethylsilane
- Stearoxytrimethylsilane
- Triethoxycaprylylsilane
- Trimethoxycaprylylsilane

The ingredients in this report are structurally-related silanes bearing both alkyl and alkoxyl groups. The functions of these ingredients include: binder, skin-conditioning agent – miscellaneous, skin-conditioning agent – emollient, and surface modifier.

The Panel noted positive results in dermal, oral, inhalation, and developmental and reproductive toxicity studies at test concentrations much greater than those reported to be used in cosmetics. However, studies conducted at concentrations similar to those used in cosmetics indicated that these ingredients do not damage the skin or cause other toxicities. Triethoxycaprylylsilane is reported to be used in 417 formulations at maximum concentrations up to 2.6% in suntan products.

Carbonate Salts

The Panel issued a final report with the conclusion that the following 6 ingredients are safe in the present practices of use and concentration when formulated to be non-irritating:

- Magnesium Carbonate
- Ammonium Bicarbonate
- Ammonium Carbonate
- Calcium Carbonate
- Potassium Bicarbonate*
- Potassium Carbonate

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

These carbonate salts are reported to function as absorbents, bulking agents, opacifying agents, pH adjusters, buffering agents, abrasives, and oral care agents. Magnesium Carbonate has the highest reported frequency of use, 317 cosmetic formulations, and Calcium Carbonate has the highest maximum concentration of use, 35% in leave-on products.

The Panel initially expressed concern about the potential for skin and ocular irritation from exposures to carbonate salts because study data indicated that Potassium Bicarbonate was mildly irritating to the abraded skin (but not intact skin) of rabbits, and potash hydrate (surrogate chemical for Potassium Carbonate) and sodium carbonate monohydrate (surrogate chemical for Potassium Carbonate) were skin and ocular irritants in rabbits, respectively. These concerns were addressed by additional studies demonstrating that Calcium Carbonate was negative for skin irritation in vivo, and Ammonium Bicarbonate, Ammonium Carbonate, Calcium Carbonate, and Magnesium Carbonate were negative for skin irritation in vitro. Study results also indicated that Magnesium Carbonate and Ammonium Bicarbonate were positive and negative, respectively, for ocular irritation in vitro and Ammonium Carbonate, Calcium Carbonate, Magnesium Carbonate, and Potassium Bicarbonate were negative for ocular irritation in vivo. The Panel noted that the carbonate salts alone would not likely be irritating at concentrations used in cosmetic products. However, these ingredients may contribute to the irritation potential of other ingredients in cosmetic formulations. Thus, the Panel determined that cosmetic products containing carbonate salts should be formulated to be non-irritating.

The Panel noted studies that reported renal toxicity and neoplastic lesions of the urinary bladder in animals fed Potassium Bicarbonate. However, the Panel concluded that the effects reported in these studies are attributable to irritation of the bladder lining after repeated daily exposure to high dietary concentrations of Potassium Bicarbonate over an extended period. The Panel agreed that the dietary exposures tested in these studies do not reflect the much lower exposures that can reasonably be expected from the use of carbonate salts in cosmetic products.
Pertinent toxicity data on ammonium carbamate was added to the report because the ingredient named Ammonium Carbonate is a mixture of ammonium bicarbonate and ammonium carbamate. Industry reported that the Cosmetic Ingredient Dictionary and Handbook (Dictionary) monograph on Ammonium Carbonate has been revised to include a CAS number [(8000-73-5 (mixture)] that represents the mixture.

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

The Panel issued a final report with the conclusion that the following 33 ingredients are safe in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing:

- Citrus Aurantifolia (Lime) Flower Extract
- Citrus Aurantifolia (Lime) Leaf Oil*
- Citrus Aurantium Amara (Bitter Orange) Flower Extract
- Citrus Aurantium Amara (Bitter Orange) Flower Oil
- Citrus Aurantium Amara (Bitter Orange) Flower Water
- 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) Wax
- Citrus Aurantium Dulcis (Orange) Leaf Extract
- Citrus Aurantium Bergamia (Bergamot) Leaf Extract
- Citrus Aurantium Bergamia (Bergamot) Leaf Oil
- Citrus Aurantium Dulcis (Orange) Extract
- Citrus Aurantium Dulcis (Orange) Seed Extract
- Citrus Aurantium Dulcis (Orange) Seed Oil
- Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract*
- Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil
- Citrus Aurantium Dulcis (Orange) Seed Extract
- Citrus Aurantium Dulcis (Orange) Seed Oil
- Citrus Aurantium Sinensis Powder
- Citrus Aurantium Sinensis Powder
- Citrus Grandis (Grapefruit) Leaf Extract*
- Citrus Depressa Flower Water*
- Citrus Grandis (Grapefruit) Leaf Extract*

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

The Panel noted that certain cultivars of Citrus reticulata leaf oil may contain approximately 50% methyl-N-methylanthranilate (or dimethyl anthranilate), which is phototoxic. The International Fragrance Association (IFRA) and the European Union’s Scientific Committee on Consumer Safety (SCCS) have issued a limit on this constituent of 0.1% in leave-on products. The maximum reported concentration of use for Citrus Reticulata (Tangerine) Leaf Oil in a leave-on product has been reported as 0.1%. Because the potential concentration of methyl-N-methylanthranilate in this ingredient would be below the limit established by IFRA and the SCCS, the Panel determined that there are no safety concerns regarding the use of Citrus Reticulata (Tangerine) Leaf Oil in cosmetics.

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

The Panel issued a final report with the conclusion that the following 18 ingredients are safe 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 Aurantium Dulcis (Orange) Seed Oil
- Citrus Aurantium Sinensis Powder
- Citrus Aurantium Sinensis Powder
- Citrus Grandis (Grapefruit) Leaf Extract
- Citrus Grandis (Grapefruit) Seed Extract
- Citrus Depressa Flower Oil*
- Citrus Grandis (Grapefruit) Leaf Extract*
- Citrus Junos Extract
- Citrus Junos Seed Extract
- Citrus Junos Seed Oil
- Citrus Nobilis (Mandarin Orange)
- Citrus Nobilis (Mandarin Orange) Oil
- Citrus Paradis (Grapefruit) Seed Extract
- Citrus Reticulata (Tangerine) Extract
- Citrus Sunki Seed Extract*
- Citrus Sunki Seed Oil*
- Citrus Iyo Oil*
- Citrus Limon (Lemon) Flower/Leaf/Stem Extract
- 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. 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 determine the safe use of these 12 ingredients are:

- Method of manufacturing
- Chemical composition and impurities
• Irritation and sensitization

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

The Panel determined that the conclusion of safe with the listed qualifications could be extended to Citrus Grandis (Grapefruit) Extract, Citrus Junos Extract, Citrus Nobilis (Mandarin Orange), Citrus Nobilis (Mandarin Orange) Oil, and Citrus Reticulata (Tangerine) Extract because these ingredients are largely used in rinse-off formulations at very low concentrations. The ingredients Citrus Jabara Pericarp Extract and Citrus Unshiu Pericarp Extract have been removed from this report and administratively added to the Citrus Peel-Derived Ingredients report because it was determined that these ingredients are alternate names for Citrus Jabara Peel Extract and Citrus Unshiu Peel Extract (ingredients which are already recited in that report).

**Dialkyl Carbonates**

The Panel issued a final report with a conclusion that the following 6 ingredients are safe in the present practices of use and concentration when formulated to be non-irritating:

- Dicaprylyl Carbonate
- Bis-Propylheptyl Carbonate*
- C14-15 Dialkyl Carbonate
- Diethylhexyl Carbonate
- Dimethyl Carbonate*
- Dipropyl Carbonate*

*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 alkyl diesters of carbonic acid mainly function as skin conditioning agents in cosmetic products; dimethyl carbonate functions as a fragrance ingredient, propellant, or solvent. Dicaprylyl Carbonate has the highest frequency of use (384 formulations) and the highest maximum concentration of use, 34.5% in leave-on products.

The Panel agreed that data on propylheptyl caprylate can be used to evaluate the following toxicity endpoints for Propylheptyl Carbonate: acute dermal toxicity, acute oral toxicity, subchronic oral toxicity, genotoxicity, skin irritation, skin sensitization, and ocular irritation. Additionally, the Panel reaffirmed their concerns about one immunotoxicity study on dimethyl carbonate; they determined that the results of the study are contradictory.

Toxicology data on 2-ethylhexanol (a hydrolysis product of Diethylhexyl Carbonate) were included in the report to assess the safety of Diethylhexyl Carbonate. An animal study reported positive embryotoxicity and teratogenicity in test animals exposed to test materials containing 2-ethylhexanol at the highest dosages but not at the lower dosage tested. The Panel agreed that the exposures tested that produced positive results are much greater than can reasonably be expected from the use of Dialkyl Carbonate in cosmetic products. The Panel also noted that Dicaprylyl Carbonate was negative in a chromosomal aberration test, which indicated the absence of excess DNA methylation.

The Panel expressed concern about the irritation potential of dialkyl carbonates. Although some studies of this ingredient reported slight to well-defined irritation in animals, a study using a 31% test solution of Dicaprylyl Carbonate had very low cutaneous irritation potential.

**PEG Propylene Glycol Derivatives**

The Panel issued a final amended report for public comment with the conclusion that the following 7 ingredients are safe as used in the present practices of use and concentrations:

- PEG-25 Propylene Glycol Stearate
- PEG-75 Propylene Glycol Stearate*
- PEG-120 Propylene Glycol Stearate*
- PEG-10 Propylene Glycol*
- PEG-8 Propylene Glycol Cocoate
- PEG-55 Propylene Glycol Oleate
- PEG-6 Propylene Glycol Caprylate/Caprate*

*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 opened this safety assessment for re-review because of the substantial increase in the number of reported uses of PEG-55 Propylene Glycol Oleate since the original safety assessment was published in 2001. There were no reported uses for this ingredient in the 2001 safety assessment. However, according to Food and Drug Administration (FDA) Voluntary Cosmetic Reporting Program (VCRP) data submitted in 2016, PEG-55 Propylene Glycol Oleate is reported to now be used in 149 formulations. The frequency of use of the other ingredients has decreased or remained at zero. The highest maximum concentration of use has decreased from 10% to 2%. The Panel reiterated that the restriction in the original report, which states that ingredients containing PEGs should not be used on damaged skin, is no longer warranted because the data on PEGs reviewed in 2010 supported the conclusion that there was no safety concern associated with using cosmetic products containing PEGs on damaged skin.

In the original safety assessment, the Panel relied on data from CIR reports on related ingredients and moieties and component parts of these ingredients to support the evaluation of the limited data on these ingredients. In the current assessment, they reaffirmed that this approach is appropriate for determining the safety of these ingredients.
Saccharide Esters

The Panel issued a final report with the conclusion that the following 40 saccharide ester ingredients are safe in the present practices of use and concentration:

- Glucose Pentaacetate*
- Maltitol Laurate
- Raffinose Isostearate*
- Raffinose Myristate*
- Raffinose Oleate*
- Sucrose Acetate Isobutyrate
- Sucrose Acetate/Stearate
- Sucrose Benzoate
- Sucrose Cacoate
- Sucrose Dipalmitate
- Sucrose Distearate
- Sucrose Hexaerucate*
- Sucrose Hexaoleate/Hexapalmitate/Hexastearate
- Sucrose Hexapalmitate*
- Sucrose Laurate
- Sucrose Myristate
- Sucrose Octaacetate*
- Sucrose Oleate*
- Sucrose Palmitate
- Sucrose Palmitate/Stearate or Sucrose Stearate-Palmitate Ester
- Sucrose Polybehenate
- Sucrose Polyololate*
- Sucrose Polylaurate
- Sucrose Polyoleate
- Sucrose Polysoyate
- Sucrose Polystearate
- Sucrose Stearate
- Sucrose Tetrahydroxystearate*
- Sucrose Tetrastearate Triacetate
- Sucrose Tribenenate*
- Sucrose Trilaurate
- Sucrose Tristearate
- Trehalose Isostearate Esters
- Trehalose Undecylenoate
- Xylitol Sesquicaprylate*

*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 discussed the data gaps for some of these ingredients. The similarities in chemical structures and in the reported functions and concentrations of use in cosmetics of the saccharide ester ingredients enabled the Panel to extrapolate or interpolate (read-across) the available safety data on some of the ingredients to address the ingredients with data gaps. For example, the data available for Sucrose Polybehenate were used to assess the potential for dermal irritation and sensitization of the single-chain length saccharide esters; multiple-endpoint data for Sucrose Acetate Isobutyrate and dermal irritation and sensitization data for Sucrose Polycottonseedate were used to assess the safety for the mixed-chain length saccharide esters.

The Panel noted that Sucrose Acetate Isobutyrate has a lower molecular weight, and therefore, greater potential for oral and dermal absorption, and thus would have a greater potential to exert biological effects than most of the ingredients for which it was used as a read-across analog. The Panel also noted the use of several of the saccharide esters as direct and indirect food additives, especially the GRAS (generally recognized as safe) status of Sucrose Acetate Isobutyrate for use as a direct food additive and determined that these uses allayed their concerns about the possibility of systemic effects from the potential oral or dermal absorption of these ingredients.

Tentative Safety Assessments

Tentative and revised tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before December 16, 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 February 17, 2017. The updated reports may be scheduled for review by the CIR Expert Panel at its April 10-11, 2017 meeting.

Butyl Polyoxyalkylene Ethers

The Panel issued a tentative amended report for public comment with the conclusion that the following 46 butyl polyoxyalkylene ethers are safe as used when formulated to be non-irritating:

- PPG-2-Buteth-1*
- PPG-2-Buteth-2*
- PPG-2-Buteth-3*
- PPG-3-Buteth-5*
- PPG-4-Buteth-4*
- PPG-5-Buteth-5
- PPG-5-Buteth-7*
- PPG-7-Buteth-4
- PPG-7-Buteth-10
- PPG-9-Buteth-12
- PPG-10-Buteth-9*
- PPG-12-Buteth-12*
- PPG-12-Buteth-16
- PPG-15-Buteth-20
- PPG-17-Buteth-17
- PPG-19-Buteth-19*
- PPG-20-Buteth-30*
- PPG-24-Buteth-27*
- PPG-26-Buteth-26
- PPG-28-Buteth-35
- PPG-30-Buteth-30*
- PPG-33-Buteth-45
- PPG-36-Buteth-36*
- PPG-38-Buteth-37
- PPG-2 Butyl Ether
- PPG-3 Butyl Ether*
Twenty-three of these ingredients were reviewed previously; 4 were reviewed in 2000 and found to be safe as used and 19 were reviewed in 2001 and found to be safe when formulated to avoid irritation. The conclusion reached at this meeting supersedes the conclusion reached in 2000 for PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-33.

In a European Chemicals Agency (ECHA) dossier on [(Butoxymethylethoxy)methylethoxy]propan-1-ol, the CAS No. for this ingredient is the same as the CAS No. given in the Dictionary for PPG-3 Butyl Ether, even though these ingredients have different chemical structures. The Panel stated that chemical and physical properties and metabolism of these two compounds should be essentially identical and, therefore, the information included in the ECHA dossier is useful for read-across. The Panel also found it appropriate to include data on 1-(2-butoxy-1-methylethoxy)-propan-2-ol because this compound is a potential metabolite of some of the ingredients and therefore strengthens the toxicology profile. However, the Panel did not consider the data on PPG-3 methyl ether and on methoxyisopropanol to be needed for read-across in this assessment.

Because of the potential for dermal irritation, the Panel specified that products containing these ingredients must be formulated to be non-irritating. Also, some of the ingredients in this group are ethoxylated; therefore, the Panel specified that industry should use good manufacturing practices to minimize the formation of nitrosamines, and eliminate the presence of impurities (i.e., 3,4-methylenedioxy-aniline) that are N-nitrosated or contain nitrosating agents. Consequently, hair dye formulations containing Hydroxyethyl-3,4-Methylenedioxanilinae HCl should not contain nitrosating agents. The Panel concurs with the limit stated in the 2009 Scientific Committee on Consumer Safety Opinion and physical properties and metabolism of these two compounds should be essentially identical and, therefore, the information included in the ECHA dossier is useful for read-across. The Panel also found it appropriate to include data on 1-(2-butoxy-1-methylethoxy)-propan-2-ol because this compound is a potential metabolite of some of the ingredients and therefore strengthens the toxicology profile. However, the Panel did not consider the data on PPG-3 methyl ether and on methoxyisopropanol to be needed for read-across in this assessment.

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Ethers and Esters of Ascorbic Acid

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

- Tetrahexyldecyl Ascorbate
- Ascorbyl Isostearate*
- Ascorbyl Linoleate
- Ascorbyl Tetraisopalmitate
- Ascorbyl Palmitate
- Ascorbyl Dipalmitate
- Ascorbyl Stearate

*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 reported to function in cosmetics products as antioxidants, skin-conditioning agents, and skin protectants. Ascorbyl Palmitate is also reported to function as a fragrance ingredient, and Ascorbyl Linoleate as a skin bleaching agent. Skin bleaching is a drug function, not a cosmetic function. Therefore, the Panel did not evaluate safety for skin bleaching.

A study reported that Ascorbyl Palmitate strongly promoted UVB-induced lipid peroxidation in human keratinocyte cultures, and the author suggested that Ascorbyl Palmitate may intensify skin damage by this mechanism following exposures to UV radiation. However, the Panel characterized the results of this study as an artifact of an irrelevant model, and disagreed with the author’s interpretation of the results. Furthermore, the results of this study were not consistent with the results of a clinical study in which topical application of Ascorbyl Palmitate prior to UVB exposures resulted in decreased or no erythema (3% Ascorbyl Palmitate cream) or enhanced resolution of UVB-induced erythema (5% Ascorbyl Palmitate cream).

The Panel noted the absence of data on developmental and reproductive toxicity, but agreed that pertinent data on ascorbic acid, mono- and di-acyl-saccharides, and mono- and di-acyl-glycols from prior CIR safety assessments would address any safety concerns.

The Panel also noted the positive results in an animal sensitization test for Ascorbyl Tetraisopalmitate. However, negative results in a human skin sensitization study for Ascorbyl Tetraisopalmitate and a human maximization study for Ascorbyl Dipalmitate alleviated their concerns.

Because the Dictionary included use as a skin bleaching agent as a possible function of Ascorbyl Linoleate, the Panel noted that Ascorbyl Linoleate must not have this effect at use concentrations in cosmetic products.

Hydroxyethyl-3,4-Methylenedioxanilinae HCl

The Panel issued a tentative report for public comment with the conclusion that Hydroxyethyl-3,4-Methylenedioxanilinae HCl is safe as a hair dye ingredient in the present practices of use and concentration.

VCRP data submitted in 2016 indicate 67 uses of this hair colorant ingredient. The Industry survey (2016) reported maximum use concentrations ranging from 0.52% to 0.75% in hair dyes and colors. Hydroxyethyl-3,4-Methylenedioxanilinae HCl contains a free, secondary aromatic substituted amine group (aniline derivative), which warrants concerns about the potential for N-nitrosation. The Panel recommended that manufacturers formulate products to reduce the formation of nitrosamines, and eliminate the presence of impurities (i.e., 3,4-methylenedioxy-aniline) that are N-nitrosated or contain nitrosating agents. Consequently, hair dye formulations containing Hydroxyethyl-3,4-Methylenedioxanilinae HCl, and formulations intended for admixture with this ingredient, should not contain nitrosating agents. The Panel concurs with the limit stated in the 2009 Scientific Committee on Consumer Safety Opinion.
Report on Hydroxyethyl-3,4-Methylenedioxyaniline HCl, issued by the European Commission, that nitrosamine content for this hair dye ingredient should be < 50 ppb.

Many hair dyes, including Hydroxyethyl-3,4-Methylenedioxyaniline HCl, are potential skin sensitizers. This ingredient is considered to be a coal tar hair dye for which regulations require caution statements and instructions for consumer patch testing (for skin irritation/sensitization) to exempt the dye from adulteration and color additive provisions of the United States Federal Food, Drug, and Cosmetics Act.

**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 February 17, 2017. These reports may be scheduled for review by the CIR Expert Panel at its April 10-11, 2017 meeting.*

**Monoalkylglycol Dialkyl Acid Esters**

The Panel issued an insufficient data announcement for this safety assessment. The 28 monoalkylglycol dialkyl acid esters included in this report are:

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<th>Ingredient</th>
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<tr>
<td>Trimethyl Pentanyl Diisobutyrate</td>
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<tr>
<td>Butylene Glycol Dicaprylate/Dicaprate</td>
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<tr>
<td>Butylene Glycol Diisononanoate*</td>
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<tr>
<td>Diethylpentanediol Dineopentanoate</td>
</tr>
<tr>
<td>Dioctadecanyl Didecyltetradecanoate*</td>
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<tr>
<td>Dioctadecanyl Ditradecyloctadecanoate*</td>
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<tr>
<td>Glycol Dibehenate*</td>
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<td>Glycol Diethylhexanoate</td>
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<tr>
<td>Glycol Dipalmate/Palm Kernelate/Olive/Macadamiate*</td>
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<tr>
<td>Glycol Dipalmate/Neopentyl Glycol Diisononanoate</td>
</tr>
<tr>
<td>Glycol Dipalmate/Rapeseedate/Soyate*</td>
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<td>Glycol Dipivalate*</td>
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<td>Glycol Distearate</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.

The additional data needed to determine the safe use of these ingredients are:

- Dermal penetration for Diethylpentanediol Dineopentanoate, Dioctadecanyl Didecylditetradecanoate, and Dioctadecanyl Ditradecyloctadecanoate.
- If there is dermal absorption for any of the three ingredients specified in the previous bullet, then: 28-day dermal toxicity, genotoxicity, and irritation and sensitization at maximum concentration of use or greater (≥57%).
- Because these ingredients can potentially form ester hydrolysis products, toxicity data on the hydrolysis products of these three ingredients including:
  - Diethylpentanediol Dineopentanoate
    - Ethylpentanediol
    - Neopentanoic Acid
  - Dioctadecanyl Didecylditetradecanoate
    - Octadecanol
    - Decyltetradecanoic Acid
  - Dioctadecanyl Ditradecyloctadecanoate
    - Tetradecyloctadecanoic Acid

The Panel removed 1,4-Butanediol Bisdecanoate and 1,2-Hexanediyl Dicaprate from the report because their only reported function (in the Dictionary) is as a skin bleaching agent. Skin bleaching agent is not a cosmetic function. The Panel also removed Butylethylpropanediol Dimer Dilinoleate because it could not be determined whether the chemical structure of this ingredient is similar to those of the other ingredients in the group.

**Persulfates**

The Panel issued an insufficient data announcement for the following 3 ingredients:

- Ammonium Persulfate
- Potassium Persulfate
- Sodium Persulfate

The Expert Panel agreed that the original report (published in 2001) on the 3 Persulfates should remain reopened to evaluate the safety of these ingredients in leave-on products and dentifrices.
The additional data needed to evaluate the safety of these ingredients in leave-on products and dentifrices are:

- No-Observed-Effect-Level (NOEL) for sensitization and urticaria
- Concentrations of use in leave-on products and dentifrices.

The original report (published in 2001) concluded that the 3 persulfates are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. The Panel agreed that this conclusion remains valid for the stated uses. The 2016 survey data indicates uses in additional leave-on product categories (e.g., eye makeup preparations, tonics, dressings, and other hair grooming aids) and in dentifrices (rinse-off). The FDA confirmed that the uses of Sodium Persulfate in dentifrices, which are toothpastes that are applied to “real teeth” and the uses of persulfates in dental cleansers, which are classified as medical devices. An FDA public health notification was issued regarding the risk of allergic reactions in users of denture cleansers containing Sodium Persulfate, and the risks of misusing these products. They noted the literature and research suggesting that the ingredient in denture cleansers responsible for these reactions is persulfate, which is a known allergen. Thus, the Panel reopened the original report on Ammonium Persulfate, Potassium Persulfate, and Sodium to evaluate the safety of these ingredients for the newly reported uses.

Additionally, the Panel restated their previous recommendation that the language in the original conclusion relating to brief and discontinuous use followed by thorough rinsing from the hair and skin be applied to users of these products such as hairdressers.

**Plant-Derived Proteins and Peptides**

The Panel reviewed the following 19 ingredients and found the data were insufficient to determine safety of one ingredient:

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

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

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

The Panel determined that the data were sufficient to support safety of the remaining 18 plant-derived protein and peptide ingredients in the present practices of use and concentration. The Panel acknowledged that Type I immediate hypersensitivity reactions could possibly occur following exposure to a protein-derived ingredient. Traditional HRPTs and related test data do not detect Type I reactions. Thus, the Panel recommends that people with known allergies to tree nut, seed, and avocado proteins avoid using personal care products that contain these ingredients.

**141st Meeting Notes**

**Director’s Report**

At the September 2016 meeting, the Council suggested an update on the scientific and regulatory issues surrounding the topic of substances with potential endocrine disrupting activities. Dr. Ellen Mihaich presented a briefing titled “Of Lists and Legends: An Endocrine Disruptor Update.” Dr. Gill, and the Panel, expressed appreciation to Dr. Mihaich for her thoughtful and comprehensive update on endocrine disruption. Dr. Mihaich is the owner and principal scientist of Environmental and Regulatory Resources, LLC (ER’ and an adjunct faculty member at Duke University.

Dr. Gill highlighted some of the many accomplishments of the Expert Panel and CIR Staff in 2016. As of October 1, the Panel assessed the safety of over 460 ingredients, with the following conclusions: 34 safe, 408 safe with qualifications, 5 with split decisions of safe with qualifications and insufficient data, and 14 with insufficient data. When the 2016 CIR Compendium is published in early 2017, it will reflect the review of over 4500 ingredients. In 2014, 8 ingredients had insufficient data to make a safety determination. In accordance with the CIR Procedures, 7 Camellia sinensis-derived ingredients, and the ingredient Avena Sativa (oat) Meristem Cell Extract will be categorized as No Reported Use at the end of December 2016; no new data were received and none of these ingredients are listed as in use in the VCRP data. In 2017, 3 ingredients (Hydrolyzed Carrageenan, MEA Hydrolyzed Silk, and Silk Cocoon Extract) were found to have insufficient data to determine safety; these ingredients are scheduled to be categorized as Use Not Supported by Data or No Reported Use at the end of 2017 if additional data are not submitted by the end of next year.

Dr. Gill also restated the announcement made on the first day of the Panel meeting that the Panel discussion of the Lead Acetate strategy would be tabled at this meeting to allow for CIR review of additional information that arrived just before the Panel meeting.
Lastly, Dr. Gill reminded the meeting participants that the next meeting is scheduled for April 10-11, 2017. 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 April 2017 meeting, to provide that data as soon as possible. All 2017 Panel meetings will be held at the Hamilton Crowne Plaza Hotel, in Washington, D.C.

Presentation on Endocrine Disruption Issues and Methods

Dr. Mihaich presented the World Health Organization (WHO) International Program on Chemical Safety (IPCS) definition of an endocrine disruptor. By this widely accepted definition, endocrine disruptors cause adverse health effects in living organisms specifically by altering the function of the endocrine system. Endocrine disruption is distinct from endocrine activity, which is simply the ability of a chemical to interact with the endocrine system without necessarily posing a health risk. Dr. Mihaich emphasized that less rigorous definitions of endocrine disruptors has had regulatory consequences, where substances have been banned based on the assessment of hazard (i.e., capability to cause harm) rather than risk (i.e., probability of causing harm under specified exposure conditions).

As noted in her presentation, the legislative mandates of the 1996 Food Quality Protection Act (FQPA) and amendments to the Safe Drinking Water Act (SDWA) led to the establishment of the U.S. EPA Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC). The EDSTAC developed the conceptual framework that provides the structure for screening (Tier 1) and testing (Tier 2) for endocrine disruptors under the U.S. EPA Endocrine Disruptor Screening Program (EDSP).

Dr. Mihaich outlined the critical elements of a weight-of-evidence (WoE) assessment. She noted the importance of evaluating the consistent pattern of responses across studies for or against explicitly defined hypotheses. She also explained how the concept of the Adverse Outcome Pathway (AOP) can be used to enhance the development and presentation of a WoE analysis, and how acute-to-chronic ratios (ACRs) can be used to help determine whether the endocrine-mediated effects of a chemical at chronic low doses or concentrations can be attributed to primary interactions of the chemical with the endocrine system.

Dr. Mihaich noted the proliferation of lists of substances that have been suggested to be endocrine disruptors or potential endocrine disruptors and the potential downsides of using such lists without considering factors such as the different purposes for which they were developed, specificity for potentially endocrine-active chemicals, differences in methodologies and criteria, appropriate requirements for data quality, or the weight of the evidence. She discussed two WHO reports on the state of the science on endocrine disrupting chemicals.


Scientific Literature Reviews

• Draft reports of the following literature reviews that are currently posted on the CIR website (http://www.cir-safety.org/ingredients/), along with any unpublished data submitted by interested parties, may be presented to the Panel at its meeting on April 10-11, 2017.

Alkane Diols
*Humulus lupus* (Hops)-Derived Ingredients

• These Scientific Literature Reviews are currently under development and may be presented to the Panel during the first half of 2017.

Ammonium Hydroxide & Ammonia
Benzyl Salicylate
Brown Algae Ingredients
Cyclic Polyl Phosphates
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
Panthenol, Pantothenic Acid, and Derivatives
Polyaminopropyl Biguanide
Polysilsesquioxanes
Polyurethanes
Triphenyl Phosphate
Zinc Salts

• The following re-reviews may be presented at the April meeting.

Lard
Parabens
Peppermint
Triglycerides
Next CIR Expert Panel Meeting

Monday and Tuesday, April 10-11, 2017, at The Hamilton Crowne Plaza Hotel, Washington, DC 20037 --- Please contact Carla Jackson (jacksonc@cir-safety.org) before the meeting if you plan to attend.