Announcement

Cosmetic Ingredient Review Expert Panel
130th Meeting (March 17-18, 2014) - Findings

March 21, 2014

● Final Safety Assessments

- **Alkyl Betaines – 11 ingredients**
- **Monosaccharides, Disaccharides, and Related Ingredients – 25 ingredients**
- **Pentaerythrityl Tetra-Di-*t*-Butyl Hydroxyhydrocinnamate – 1 ingredient**
- **Tocopherols and Tocotrienols – 14 ingredients**

● Tentative Safety Assessments

- **Barium Sulfate (an ingredient in Inorganic Sulfates) – 1 ingredient**
- ***Camellia sinensis*-Derived Ingredients – 14 ingredients**
- **Fatty Acid Amidopropyl Dimethylamines – 24 ingredients**
- **Hydrolyzed Wheat Gluten and Hydrolyzed Wheat Protein – 2 ingredients**
- **Hydroquinone – 1 ingredient**
- ***p*-Hydroxyanisole – 1 ingredient**
- **Magnesium Sulfate (an ingredient in Inorganic Sulfates) – 1 ingredient**
- **PEG-150 Pentaerythrityl Tetrastearate – 1 ingredient**
- ***Rosmarinus officinalis* (Rosemary)-Derived Ingredients – 10 ingredients**
- **Tripeptide-1, Hexapeptide-12, their Metal Salts and Fatty Acyl Derivatives, and Palmitoyl Tetrapeptide-7– 10 ingredients**

● Insufficient Data Announcements

- **None**

● Re-review Summaries

- **Alpha-Hydroxy Acids – approved**
- **Sodium α-Olefin Sulfonates – approved**

● 130th Meeting Notes

- **Director's report**
- **Hydrolyzed Wheat Protein/Gluten Briefings**
- **Reports tabled**
  - **Polyoxyalkylene Siloxane Copolymers, Alkyl-Polyoxyalkylene Siloxane Copolymers, and Related Ingredients– 111 ingredients**
  - **Citrus-Derived Ingredients – 198 ingredients**
  - **Methylisothiazolinone – 1 ingredient**
- **2015 Review Priorities**
- **Scientific Literature Reviews**
  - **Posted on the CIR website**
    - **Ceramides**
    - ***Avena sativa* (Oat)-derived ingredients**
    - **Alkyl Phosphates**
    - **Styrene and Vinyl-type Styrene Copolymers**
    - **2-Amino-3-Hydroxypyridine**
  - **Under development**
    - **Polyene group**
    - **Inorganic Hydroxides**
    - **Glycerin**
    - **Sodium Benzotriazolyl Butylphenol Sulfonate**

        - **PEGylated Alkyl Glyceride**
        - **Plant Polysaccharide Gums**
        - ***Centella asiatica*-derived ingredients**

- **Re-reviews for the next Panel meeting**
    - **Polyvinyl Alcohol – 1 ingredient**

- **Next CIR Expert Panel Meeting – Monday and Tuesday, June 9-10, 2014**

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 Unpublished data cited as references in CIR safety assessments are available for review.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

Alkyl Betaines

The Panel issued a final safety assessment on alkyl betaines with the conclusion that the 11 ingredients listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

betaine
behenyl betaine
cetyl betaine
coco-betaine
decyl betaine*
lauryl betaine
myristyl betaine
oleyl betaine
stearyl betaine
tallow betaine*
hydrogenated tallow betaine*

*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.

Data available to the Panel on alkyl betaines, indicated low systemic toxicity at high doses in single-dose and repeated-dose oral animal studies, no teratogenic or carcinogenic effects in animal studies, no genotoxicity in *in vitro* and *in vivo* studies, and no sensitization in multiple tests. The Panel indicated that most surfactants exhibit some irritancy, as was found in dermal and ocular studies of coco-betaine, lauryl betaine, and a betaine analog. Thus, the Panel concluded that products containing the ingredient in this report should be formulated to be non-irritating.

The Panel noted the absence of data on the UV absorption or phototoxicity of alkyl betaines. However, none of the molecules that comprise these ingredients are chromophores, and the Panel concluded that these ingredients are not phototoxic.

The Panel expressed concern about the dangers inherent in using animal-derived ingredients (i.e., tallow), specifically the potential for transmission of infectious agents. They emphasized that these ingredients must be free of detectable pathogenic viruses and other infectious agents (e.g., bovine spongiform encephalopathy (BSE) prion). These ingredients should be produced in accordance with current good manufacturing practices (cGMPs) and should conform to regulations for producing substances from animal-derived materials.

The Panel also expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. The cosmetics industry should continue to use cGMPs to limit impurities, the Panel stated.

Monosaccharides, Disaccharides, and Related Ingredients

The Panel issued a final safety assessment with the conclusion that the following 25 monosaccharides, disaccharides, and related ingredients are safe in the present practices of use and concentration in cosmetics:

calcium gluconate
fructose
fucose*
galactose*
galactosyl fructose*
galacturonic acid*
gluconic acid
glucose
isomalt
kefiran
lactitol
lactose
lactulose*
maltose
mannose
melibiose
potassium Gluconate
rhamnose
ribose
sodium gluconate
sucralose
sucrose
trehalose
xylobiose
xylose

*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 mostly as skin conditioning agents. Other functions reported include use as humectants or flavoring agents.

Mono- and disaccharides are simple very hydrophilic sugars that readily dissolve in aqueous solvent systems. Many of the ingredients in this report are common dietary sugars, dietary sugar replacements, or very closely related analogs and salts. Several are generally recognized as safe (GRAS) food additives or direct food additives. Because the oral safety of these ingredients has been well-documented, systemic toxicity was not a concern of the Panel.

This report covers some ingredients that are not GRAS food substances or direct food additives but are listed in the *Food Chemicals Codex* as having a function in foods, in the *Everything Added to Foods in the United States (EAFUS)* inventory, and/or listed as an inactive ingredient in oral drugs. The leave-on use concentrations of these ingredients are typically less than 1%. The Panel discussed the limited oral and reproductive toxicity data. They determined that systemic toxicity was not likely because of the low concentrations of use of these ingredients and limited systemic exposures that can be

expected from dermal applications. Irritation was reported during the induction phase of a sensitization study of a hair product containing 29% sucrose (diluted to 50% for testing). However, the Panel stated that this was attributable to the surfactant properties of the product, and not due to the sucrose.

Pentaerythrityl Tetra-Di-*t*-Butyl Hydroxyhydrocinnamate

The Panel issued a final safety assessment with the conclusion that pentaerythrityl tetra-di-*t*-butyl hydroxyhydrocinnamate is safe in the present practices of use and concentration in cosmetics.

Percutaneous absorption is not expected for this cinnamate tetraester of pentaerythritol because of its octanol-water partition coefficient and high molecular weight. Pentaerythrityl tetra-di-*t*-butyl hydroxyhydrocinnamate is currently used in leave-on products at concentrations up to 0.8%. The Panel noted the absence of percutaneous absorption potential and negative results in oral reproductive and developmental toxicity oral carcinogenicity studies and in human skin sensitization studies at a concentration of 0.5%. The Panel concluded that using pentaerythrityl tetra-di-*t*-butyl hydroxyhydrocinnamate as an antioxidant in cosmetic products does not present a safety concern.

The Panel discussed the potential for incidental inhalation exposure to this ingredient in products that are sprayed or are in powder form and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone, ingredient use concentrations, and negative acute oral toxicity studies, incidental inhalation would not lead to local respiratory or systemic effects.

Tocopherols and Tocotrienols

The Panel issued a final amended safety assessment with the conclusion that the following 14 ingredients are safe in the present practices of use and concentration in cosmetics.

tocopherol
tocopheryl acetate
tocopheryl linoleate
tocopheryl linoleate/oleate
tocopheryl nicotinate
tocopheryl phosphate*
tocopheryl succinate
ascorbyl tocopheryl acetate*
ascorbyl tocopheryl maleate
dioleyl tocopheryl methylsilanol
potassium ascorbyl tocopheryl phosphate
sodium tocopheryl phosphate
tocophersolan
tocotrienols

*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 tocopherols are reported to function in cosmetics as antioxidants or skin conditioning agents. Tocotrienols is reported to function as a light stabilizer, oral care agent, or skin conditioning agent. Tocopherols and tocotrienols are amphiphilic lipids that, together, comprise vitamin E. Both are GRAS food ingredients.

The Panel reviewed the pertinent animal and clinical data for these ingredients, and determined that it was appropriate to interpolate the existing information to assess the safety of all of the ingredients in this report. The Panel noted that epidemiology studies on the use of vitamin E supplements report both positive and negative health effects and, overall, the results are inconclusive. They noted that systemic exposures to oral vitamin E supplements will be much higher than can be expected from the use of cosmetic products containing vitamin E. Therefore, the negative health effects reported in some of the epidemiological studies were not cause for concern for the cosmetic use of these ingredients.

The Panel noted that, although moderate sensitization potential was reported in a guinea pig maximization test, dermal reactions to tocopherol in humans are rare. The North American Contact Dermatitis Group deleted this ingredient from its standard testing because of the extremely low incidence of reactions. Additionally, the Panel noted that tocopherol has some absorbance in the UVA range. However, the results of phototoxicity and photoallergenicity tests are negative.

Tentative Safety Assessments

*Tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before **March 31, 2014**. 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 by **April 18, 2014, or sooner if possible.** These reports may be scheduled for review by the CIR Expert Panel at its **June 9-10, 2014** meeting.*

Barium Sulfate (an ingredient from the Inorganic Sulfates report)

The Panel elected to reduce the Inorganic Sulfates report into two separate reports that focus on the highest frequency of use ingredients, namely magnesium sulfate and barium sulfate. Review of the remaining ingredients will be postponed until their frequency of use warrants assessment.

The Panel issued a tentative safety assessment for public comment with the conclusion that barium sulfate is safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

The Panel noted that the history of safe medical use of barium sulfate indicates no significant toxicity concerns for systemic exposures to these ingredients. Furthermore, the extensive clinical experience of the Panel, including the results of numerous patch tests, indicates that barium salts do not have the

potential to induce sensitization. The Panel noted that salts of sulfuric acid, such as sodium sulfate, can be irritating to the skin so cosmetic products containing barium sulfate should be formulated to be non-irritating.

Barium sulfate is used in leave-on products at concentrations up to 37%. In leave-on products that include powders, barium sulfate is used at concentrations up to 15.8%. The Panel discussed the potential for incidental inhalation exposures to these ingredients in products that are in powder form and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone, ingredient use concentrations, and negative results in acute oral toxicity studies, incidental inhalation would not lead to local respiratory effects (e.g., baritosis) or systemic effects.

***Camellia sinensis*-Derived Ingredients**

The Panel issued a tentative safety assessment for public comment with the conclusion that camellia sinensis leaf extract is safe up to 0.86% in leave-on products and up to 1% in rinse-off products. Camellia sinensis catechins are safe in the present practices of use and concentration described in this safety assessment.

The Panel also concluded that the available data are insufficient to assess the safety of the ingredients listed below:

camellia sinensis flower extract
camellia sinensis flower/leaf/stem juice
camellia sinensis leaf
camellia sinensis leaf oil
camellia sinensis leaf powder
camellia sinensis leaf water
camellia sinensis root extract
camellia sinensis seedcoat powder
camellia sinensis seed extract
camellia sinensis seed powder
hydrolyzed camellia sinensis leaf
hydrolyzed camellia sinensis seed extract

The data needs for these ingredients include:

- method of manufacturing;
- characterization data;
- human sensitization data, in particular for camellia sinensis leaf powder at 50%;
- concentration of use in cosmetics; and
- confirmation that camellia sinensis leaf water is used only as a fragrance.

These ingredients reportedly function as antioxidants, and skin-conditioning agents – humectant and miscellaneous in cosmetics. The *C. sinensis*-derived ingredients in this safety assessment are from plants that are used extensively in human diet. The Panel agreed that exposures to these ingredients in beverages results in much larger systemic exposures than from cosmetic uses. Thus, oral toxicity potential is not a primary concern. Reproductive toxicity, genotoxicity, and carcinogenicity data are presented in the safety assessment but, the primary focus is on the potential for irritation and sensitization.

Camellia sinensis leaf extract is reported to be used at concentrations up to 3%. The Panel determined that the HRIPT data supports a safety conclusion for products that contain this ingredient at up to 0.86%. If additional information confirms that camellia sinensis leaf water is used only as a fragrance, it will be deleted from this report.

Fatty Acid Amidopropyl Dimethylamines

The Panel issued a tentative safety assessment for public comment with the conclusion that the 24 fatty acid amidopropyl dimethylamines ingredients listed below are safe in cosmetics when they are formulated to be non-sensitizing.

almondamidopropyl dimethylamine*
avocadamidopropyl dimethylamine*
babassuamidopropyl dimethylamine*
behenamidopropyl dimethylamine
brassicamidopropyl dimethylamine
cocamidopropyl dimethylamine
dilinoleamidopropyl dimethylamine*
isostearamidopropyl dimethylamine
lauramidopropyl dimethylamine
linoleamidopropyl dimethylamine
minkamidopropyl dimethylamine
myristamidopropyl dimethylamine*
oatamidopropyl dimethylamine*
oleamidopropyl dimethylamine
olivamidopropyl dimethylamine*
palmitamidopropyl dimethylamine
ricinoleamidopropyl dimethylamine*
sesamidopropyl dimethylamine*
soyamidopropyl dimethylamine*
stearamidopropyl dimethylamine
sunflowerseedamidopropyl dimethylamine*
tallamidopropyl dimethylamine*
tallowamidopropyl dimethylamine*
wheat germamidopropyl dimethylamine*

*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, although a safe conclusion was reached for this ingredient group, 3,3-dimethylaminopropylamine (DMAPA) impurities in oleamidopropyl dimethylamine appeared to be present at a concentration higher than the DMAPA concentrations reported in other amidopropyl dimethylamines. Based on the data submitted, DMAPA impurities in oleamidopropyl dimethylamine can exceed the limit recommended by the Panel in the cocamidopropyl betaine (CAPB) safety assessment (i.e., 0.01% DMAPA when CAPB is used at the highest reported maximum use concentration). The Panel requested that industry provide additional information on DMAPA in oleamidopropyl dimethylamine.

After a robust discussion of the sensitivity studies submitted, the Panel noted that, for stearamidopropyl dimethylamine, the highest reported maximum use concentrations in leave-on products may yield DMAPA concentrations that exceed the limit for this impurity that the Panel recommended in the safety

assessment of CAPB (e.g., greater than the EC_3 value (the effective concentration of the test substance required to produce a three-fold increase in the stimulation index compared to vehicle-treated controls) from a local lymph node assay (LLNA) on stearamidopropyl dimethylamine).The Panel acknowledged that the limit is not exceeded when the concentration is estimated using a qualitative risk assessment (QRA). Industry agreed with the Panel's request to provide a QRA for stearamidopropyl dimethylamine using the weight-of-evidence no expected sensitization induction level (WoE NESIL) of 1000 $\mu g/cm^2$ and the safety test data presented in this safety assessment report.

The Panel expressed concern about the potential ability of amidopropyl dimethylamines with shorter fatty acids to be absorbed through the skin and into the systemic circulation. However, the high no observed adverse effect levels (NOAELs) in toxicity tests of amidopropyl dimethylamines with longer fatty acids alleviated this concern. The Panel felt that the overall toxicological data supported the safety of amidopropyl dimethylamines with fatty acid chain lengths C18 or higher.

Hydrolyzed Wheat Gluten and Hydrolyzed Wheat Protein

The Panel issued a revised tentative amended safety assessment of hydrolyzed wheat protein and hydrolyzed wheat gluten for public comment with the conclusion that these ingredients are safe for use in cosmetics when formulated to restrict peptides to a weight-average molecular weight (MW) of 3500 daltons (Da) or less.

The Panel reviewed data from a raw materials manufacturer and information presented by experts on the potential for exposures to hydrolyzed wheat protein in cosmetic products to cause type 1 immediate hypersensitivity reactions. Production processes involving high-heat acid hydrolysis of wheat protein/gluten may yield deamidated high-MW polypeptides with substantial potential to sensitize individuals through percutaneous and mucous-membrane exposures, especially in formulations that contain surfactants. Studies have shown that hydrolysates with average MWs < 3,000 exhibit no potential to elicit hypersensitivity reactions in sensitized individuals, in contrast to hydrolysates with average MWs >30,000 Da. The experimental results support the theory that a polypeptide must be at least 30 amino acids long to have the two IgE-binding epitopes needed to elicit type 1 hypersensitivity reactions. Thus, polypeptides with MW less than 3,000 Da do not have the potency required to induce type 1 hypersensitivity. Based on the information presented, the Panel decided that an earlier caveat that wheat gluten and wheat protein hydrolysates should not be used on damaged skin or in products that may be inhaled or applied to mucous membranes could be removed from the conclusion.

Industry requested that the Panel consider incorporating into this assessment information on wheat gluten (non-hydrolyzed), and triticum vulgare (wheat) protein and triticum vulgare (wheat) germ protein from a previous safety assessment. Because hydrolysis, particularly acid hydrolysis, can be expected to yield products that are significantly different in their chemical properties, potential bioavailability and bioactivity from the starting material, the Panel decided that these additions were not warranted.

Hydroquinone

The Panel issued a tentative amended assessment of hydroquinone for public comment with a conclusion of safe for use as a polymerization inhibitor in artificial nail coatings when photo-protective materials for the skin are used. The previous conclusion that hydroquinone is safe at concentrations of ≤1% in cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair, is safe for use in nail adhesives in the practices of use and concentration, and should not be used in other leave-on cosmetic products, was reaffirmed.

In their robust discussion about the light sources used to harden nail gels, the Panel reviewed estimates of risks of developing squamous cell carcinoma in individuals who are placing their hands under the UVA light source. The Panel's acknowledged that there is controversy about the potential mutagenicity of UVA light under the conditions of use, indicating that a slightly elevated risk of developing squamous cell carcinoma is possible. The Panel noted that the possible risk of photo-carcinogenicity warrants the precaution to use-a broad spectrum sunscreen or photo-protective covering, such as light-impermeable gloves, during the gel-curing process. Directions advising that contact with the skin and cuticle be avoided should be carefully followed by both professionals and home users of nail gels.

The Panel noted correspondence providing information that the number of uses of this ingredient is greater than that reported by the Voluntary Cosmetic Registration Program (VCRP). The Panel stated that it is important that companies report their ingredient usage to this program, as well as responding to the concentration of use surveys conducted by the Council, to facilitate the development of safety assessments based on accurate and comprehensive ingredient use information. Additionally, they requested that Industry clarify whether or to what degree ingredient usage in professional products is included in the VCRP.

***p*-Hydroxyanisole**

The Panel issued a tentative amended safety assessment of *p*-hydroxyanisole for public comment with a conclusion of safe for use as a polymerization inhibitor in artificial nail coatings when photo-protective materials for the skin are used. This ingredient is unsafe for use in all other cosmetic products because of its depigmentation properties.

In their robust discussion about the light sources used to harden nail gels, the Panel reviewed estimates of risks of developing squamous cell carcinoma in individuals placing their hands under the UVA light source. The Panel acknowledged that there is controversy about the potential mutagenicity of UVA light under the conditions of use, indicating that a slightly elevated risk of developing squamous cell carcinoma is possible. The Panel noted that the possible risk of photo-carcinogenicity warrants the precaution to use a broad-spectrum sunscreen or photo-protective covering, such as light-impermeable gloves, during the gel-curing process. Directions advising that contact with the skin and cuticle be avoided should be carefully followed by both professionals and home users of nail gels.

The Panel noted correspondence providing information that, although the VCRP does not report any uses, certain cosmetic products containing *p*-hydroxyanisole have been reported to be available for sale in the U.S. They stated that it is important that companies report their ingredient usage to this program, as well as responding to the concentration of use surveys conducted by the Council, to facilitate the development of safety assessments based on

accurate and comprehensive ingredient use information. Additionally, they requested that Industry clarify whether or to what degree ingredient usage in professional products is included in the VCRP.

Magnesium Sulfate (former an ingredient in the Inorganic Sulfates report)
The Panel elected to reduce the Inorganic Sulfates report into two separate reports that focus on the highest frequency of use ingredients, namely magnesium sulfate and barium sulfate. Review of the remaining ingredients will be postponed until their frequency of use warrants assessment.

The Panel issued a tentative safety assessment for public comment with the conclusion that magnesium sulfate is safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

The Panel noted that the history of safe medical use of magnesium sulfate indicates no significant toxicity concerns for systemic exposures to these ingredients. Furthermore, the extensive clinical experience of the Panel, including the results of numerous patch tests, indicates that magnesium salts do not have the potential to induce sensitization. The Panel noted that salts of sulfuric acid, such as sodium sulfate, can be irritating to the skin so cosmetic products containing magnesium sulfate should be formulated to be non-irritating.

Magnesium sulfate is used at concentrations up to 11%.

PEG-150 Pentaerythrityl Tetrastearate

The Panel issued a tentative safety assessment for public comment with the conclusion that PEG-150 pentaerythrityl tetrastearate is safe in the present practices of use and concentration in cosmetics.

Current use concentration data indicate that the maximum reported use concentrations of PEG-150 pentaerythrityl tetrastearate in rinse-off and leave-on products were 5% and 1.8%, respectively. Industry provided additional data on impurities and the method of manufacture during the Panel meeting. Because the method of manufacture ensures minimal formation of free PEG and the specifications for impurities limit ethylene oxide and 1, 4-dioxane to 1 ppm and 5 ppm, respectively, the Panel agreed that concerns about these impurities are not warranted for this ingredient.

Furthermore, after considering the large size of this molecule, based on its chemical structure, the Panel agreed that percutaneous absorption is not expected. The absence of the potential for percutaneous absorption and the negative results of genotoxicity and skin irritation and sensitization studies provided the Panel with a sufficient basis to assess the safety of PEG-150 pentaerythrityl tetrastearate used as a viscosity increasing agent in cosmetic products.

***Rosmarinus officinalis* (Rosemary)-Derived Ingredients**

The Panel issued a tentative amended safety assessment for public comment with the conclusion that the following eight *Rosmarinus officinalis*-derived ingredients are safe as used in cosmetics when formulated to be non-sensitizing:

rosmarinus officinalis (rosemary) extract
rosmarinus officinalis (rosemary) flower/leaf stem extract
rosmarinus officinalis (rosemary) flower/Leaf/Stem Water*
rosmarinus officinalis (rosemary) leaf
rosmarinus officinalis (rosemary) leaf oil
rosmarinus officinalis (rosemary) leaf powder
rosmarinus officinalis (rosemary) leaf water
rosmarinus officinalis (rosemary) water

*Not reported to be in current use. If this ingredient were 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.

Additionally, the Panel concluded that Rosmarinus Officinalis (Rosemary) Leaf Extract and Rosmarinus Officinalis (Rosemary) Flower Extract are safe at concentrations ≤0.2% in leave-on products, and safe as used in rinse-off products, when formulated to be non-sensitizing.

At the December 2013 meeting, the Panel concluded that the available data were insufficient to determine whether Rosmarinus Officinalis (Rosemary) Flower Extract was safe for use in cosmetics because the chemical characterization of the flower was not defined in the report. Data on the chemical characterization were found, incorporated into the report, and considered to be adequate. The Panel determined that setting a concentration limit was necessary for this ingredient because concentration of use data were not reported.

Additionally, the Panel addressed the concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent, by stating that when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. The conclusion includes the statement that products containing these botanicals must be formulated to be non-sensitizing.

Tripeptide-1, Hexapeptide-12, their Metal Salts and Fatty Acyl Derivatives, and Palmitoyl Tetrapeptide-7

The Panel issued a tentative safety assessment for public comment with the conclusion that the following 10 ingredients identified as tripeptide-1, hexapapeptide-12, their metal salts and fatty acyl derivatives, and palmitoyl tetrapeptide-7, are safe in the present practices of use and concentration in cosmetics. This conclusion is applicable only to ingredients with peptide sequences that are defined as follows: tripeptide-1 (glycine-histidine-lysine), hexapeptide-12 (valine-glycine-valine-alanine-proline-glycine *only*), and tetrapeptide-7 (glycine-glutamine-proline-arginine).

tripeptide-1
palmitoyl tripeptide-1
myristoyl tripeptide-1*
hexapeptide-12*
palmitoyl hexapeptide-12
myristoyl hexapeptide-12*
copper tripeptide-1
bis(tripeptide-1) copper acetate*
manganese tripeptide-1*
palmitoyl tetrapeptide-7

*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.

Palmitoyl hexapeptide-12 is reported to function as an antioxidant in cosmetic products; the remaining 9 ingredients reportedly function as skin conditioning agents.

These ingredients were initially included in the CIR safety assessment titled Palmitoyl Oligopeptides. This group was subsequently revised to include only ingredients with a defined peptide sequence (i.e., tripeptide-1[glycine-histidine-lysine] and hexapeptide-12 [valine-glycine-valine-alanine-proline-glycine]) bonded to a palmityl group or one of various other groups. The Panel specifically pointed out that this assessment does not apply to the other sequence listed in the INCI dictionary for hexapeptide-12 (i.e., ala-pro-gly-val-gly-val). Because of major differences in chemistry/biological activity between some of the more complex groups attached to the peptide, the Panel determined that the current safety assessment should include only tripeptide-1, hexapeptide-12 (valine-glycine-valine-alanine-proline-glycine *only*), their metal salts and fatty acyl derivatives, and palmitoyl tetrapeptide-7 (Pal-glycine-glutamine-proline-arginine). The latter ingredient was added because it is a component of one of the trade name mixtures containing palmitoyl tripeptide-1, for which safety test data are available.

During the Panel discussion, an expert research scientist in the field of cosmetic peptide chemistry commented that peptide ingredients are used in cosmetic products at concentrations between 1 ppm and 30 ppm, but concentrations < 10 ppm are customary. He also provided genotoxicity, ocular irritation, and human repeated insult patch test data on palmitoyl tetrapeptide-7. The Panel determined that, overall, the data in the safety assessment, were sufficient to support the safety of these ingredients in present practices of use and concentration in cosmetics.

Re-review Summaries

Re-review Summaries

The Panel approved the summary of their actions at the December 2013 meeting during which they determined not to reopen the safety assessment of glycolic and lactic acid, their common salts and their simple esters; and sodium α-olefin sulfonates.

130th Meeting Notes

Director's Report

Dr. Gill made an official announcement that the CIR website now provides users with the ability to search for reports by ingredient name. CIR plans to continue with improvements that expand the content and usability for all stakeholders.

Dr. Gill provided the Panel with an update on the scheduled reviews of the 17 CIR Boilerplates that are used in safety assessments. These are divided into 3 priority groups. CIR invites comments from the Panel and public on the review priorities below, and content of the boilerplate language. Draft changes, if applicable, will be provided for Panel discussion at the June meeting. The Infant Skin boilerplate is being added to the list, although the language has not been finalized by the Panel. CIR anticipates finalizing that language after the June 2014 presentations and discussion.

- High Priority: contaminants, residues, impurities, pesticides/heavy metals; formaldehyde; formats for reports; hair dyes; infant skin; read across
- Medium Priority: alternatives to 28-day dermal toxicity study; irritation potential; leave-on & rinse-off; nitrosamine; phototoxicity; usage data gaps
- Low Priority: aerosols; botanicals; pH adjusters; skin penetration studies; transmission of infectious disease

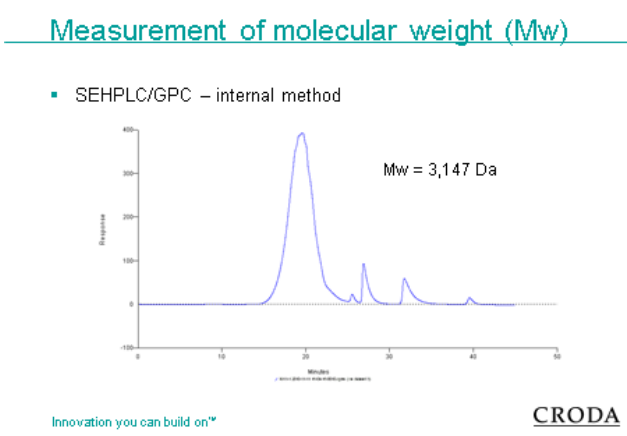
Hydrolyzed Wheat Protein/Gluten Briefings

In September of 2013, the Panel asked for experts to address the Panel's questions about type 1 immediate hypersensitivity reactions attributed to exposures to hydrolyzed wheat protein/gluten (HWP/G) in cosmetic products in Japan and Europe. On the first day of the current meeting, two speakers discussed the findings of current clinical and laboratory investigations prompted by these incidents.

Surinder P. Chahal, Ph.D., is a chemist with expertise in cosmetic proteins and Director of Research and Technology, Sun Care and Biotechnology Division, Croda Europe Ltd. He explained the principles and methods of hydrolyzing proteins and characterizing the polypeptide products of hydrolysis, and presented the results of studies on the sensitization potential of hydrolyzed wheat proteins.

Dr. Chahal noted that water insoluble ("vital") wheat gluten is prepared by washing wheat flour to remove the starch. The gluten remaining is then treated with acid to partially deamidate the proteins, which renders them dispersible ("soluble") in water. The resultant proteins have relatively high molecular weights (MWs), which can be hydrolyzed by acid, alkali or protease treatment to yield water soluble proteins or polypeptides, which can be derivatized by quaternization or copolymerization, or amino acids, depending on the method and the extent of the hydrolysis.

Dr. Chahal emphasized that there is no standard method for measuring the molecular weights (MWs) of the small polypeptides that can be produced by hydrolyzing gluten. The MWs typically are measured by Size-Exclusion High Pressure Liquid Chromatography / Gel Permeation Chromatography (SEHPLC/GPC), GPC / Multi-Angle Laser Light Scattering (MALLS), or sodium dodecyl sulfate – polyacrylamide gel electrophoresis (SDS-PAGE), and are expressed as weight-average MWs. He presented the figure on the left to illustrate the typical result of using SEHPLC/GPC to estimate the weight-average MW.



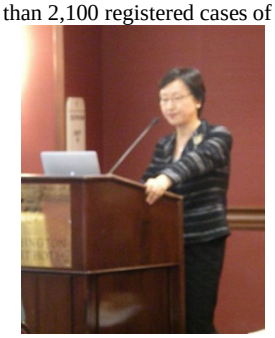
Dr. Chahal presented the results of several studies using *in vitro* methods. The results demonstrated that low-MW (~3,000 Da weight average) wheat protein hydrolysates did not bind to gluten-specific IgE antibodies, and that amino acids (~150 Da) prepared by extensive hydrolysis of wheat gluten produced no sensitization response, in contrast to the "parent" wheat protein or its high-MW (~100,000 to 125,000 Da) hydrolysates. The results indicated that extensive hydrolysis can eliminate the potential for type 1 hypersensitivity reactions to the hydrolysates.

Dr. Chahal summarized the results of skin prick tests showing no response of patients in Europe with "conventional" wheat allergy to low- or high-MW hydrolysates, demonstrating the absence of cross-reactivity in these patients. This contrasts with patients in Japan who developed contact allergy to a high-MW (50,000) deamidated acid-hydrolyzed wheat gluten preparation (Glupearl 19S) and exhibited cross-reactivity to conventional wheat products.

The evidence that Dr. Chahal presented showed that the potential for sensitization to hydrolyzed wheat gluten depends on the degree of deamidation and the MW of the hydrolysate. High-MW hydrolysates that are not deamidated (e.g., prepared enzymatically) are not sensitizing, and high-MW hydrolysates that are partially deamidated can be sensitizing. For example, Glupearl 19S (~50,000 Da) is substantially deamidated by relatively rigorous acid hydrolysis, and is a strong sensitizer, as the Japanese studies have shown. In contrast, hydrolysates with weight-average MWs of about 3,000 Da or less are not sensitizing regardless of the level of deamidation.

Kayoko Matsunaga, M.D., Ph.D., is Professor and Chair of the Department of Dermatology at the Fujita Health University School of Medicine, Japan, and Chair of the Japanese Society of Allergology's Special Committee for the Safety of Protein Hydrolysates in Cosmetics. She presented information from studies prompted by an outbreak in Japan of type 1 immediate hypersensitivity reactions to a hydrolyzed wheat gluten (HWG) ingredient (Glupearl 19S) in facial soaps and other products.

Dr. Matsunaga explained that the outbreak of hypersensitivity reactions was attributed mainly to the use of a popular soap product (*Cha no shizuku*) containing 0.3% Glupearl 19S, which has an average MW of about 50,000 Da. There are presently more than 2,100 registered cases of this type of sensitivity across Japan.



Generally, the signs of sensitization appeared 1 to 1½ years after starting to use the soap, but onset ranged from 2 months to 3 years after the start. The clinical manifestations of sensitization to Glupearl 19S include eyelid edema and contact urticaria during or after using the soap in many, but not all, of the patients. Eating foods containing wheat ingredients caused anaphylactic reactions in about 55% of these patients, including anaphylactic shock in about 25% of them. Dr. Matsunaga noted that clinical and experimental evidence indicates that these patients exhibit systemic reactions to ingested wheat products because they have been sensitized through percutaneous or mucous-membrane exposures to Glupearl 19S. Many of these patients do not exhibit eyelid edema or urticarial reactions during or after use of the product, which makes diagnosis challenging. Dr. Matsunaga outlined the diagnostic criteria developed by the Special Committee that she chairs.

Dr. Matsunaga summarized the results of experimental studies indicating that there is little chance that HWP or HWG that do not contain polypeptides greater than 30 amino acids long (MW about 3,000 Da) can induce type 1 immediate hypersensitivity. For example, hydrolysates prepared by acid hydrolysis of gluten at high temperatures (95ºC or 100 ºC) for 0 to 48 hours yields hydrolysates with average MWs ranging from < 3,000 Da to > 10,000 Da, depending on the duration of the hydrolysis. Regardless of the duration, all of the hydrolysates are about 50% deamidated by the treatment. However, hydrolysates with average MWs < 3,000 exhibit no potential to elicit hypersensitivity reactions in sensitized individuals, in contrast to hydrolysates with average MWs >30,000 Da. She explained that the experimental results clearly support the reasoning that a polypeptide must be at least 30 amino acids long to have the two IgE-binding epitopes required to elicit type 1 hypersensitivity reactions. It follows that polypeptides with MW less than 3,000 Da do not have the potency required to induce type 1 hypersensitivity.

Reports tabled

Polyoxyalkylene Siloxane Copolymers, Alkyl-Polyoxyalkylene Siloxane Copolymers, and Related Ingredients

The Panel tabled the safety assessment of polyoxalkylene siloxane copolymers, alkyl-polyoxyalkylene siloxane copolymers, and related ingredients; this report was previously named alkoxy polysiloxanes; however, the Panel determined that this name was more inclusive of the ingredients listed.

The Silicones Environmental, Health, and Safety Center committed to providing additional data to CIR. Data from other sources is also encouraged. Although the Panel did not issue an insufficient data announcement, the Panel stated that the following data are needed for this report:

- molecular weight ranges;
- impurities and how they are removed, particularly allyl alcohol ethoxylate; and
- dermal penetration, irritation, and sensitization data for the smallest ingredient(s) in this group.

The 111 ingredients included in this report are:

behenoxy dimethicone
behenoxy PEG-10 dimethicone
bis-cetyl/PEG-8 cetyl PEG-8 dimethicone
bis-hydroxyethoxypropyl dimethicone
bis-isobutyl PEG/PPG-10/7/dimethicone copolymer
bis-isobutyl PEG-13/dimethicone copolymer
bis-isobutyl PEG-24/PPG-7/dimethicone copolymer
bis-PEG-1 dimethicone
bis-PEG-4 dimethicone
bis-PEG-8 dimethicone
bis-PEG-10 dimethicone
bis-PEG-12 dimethicone
bis-PEG-12 dimethicone beeswax
bis-PEG-12 dimethicone candelillate
bis-PEG-15 methyl ether dimethicone
bis-PEG-20 dimethicone
bis-PEG-8 PEG-8 dimethicone
bis-PEG/PPG-14/14 dimethicone
bis-PEG/PPG-15/5 dimethicone
bis-PEG/PPG-16/16 PEG/PPG-16/16 dimethicone
bis-PEG/PPG-18/6 dimethicone
bis-PEG/PPG-20/20 dimethicone
bis-PEG/PPG-20/5 PEG/PPG-20/5 dimethicone
bis-stearoxy dimethicone
bis-stearoxyethyl dimethicone
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PEG/PPG-18/12 dimethicone
PEG/PPG-18/18 dimethicone
PEG/PPG-18/6 dimethicone
PEG/PPG-19/19 dimethicone
PEG/PPG-20/15 dimethicone
PEG/PPG-20/20 dimethicone
PEG/PPG-20/22 butyl ether dimethicone
PEG/PPG-20/22 methyl ether dimethicone
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PEG/PPG-3/10 dimethicone
PEG/PPG-30/10 dimethicone
PEG/PPG-4/12 dimethicone
PEG/PPG-6/4 dimethicone
PEG/PPG-6/11 dimethicone
cetyl PEG/PPG-10/1 dimethicone
cetyl PEG/PPG-15/15 butyl ether dimethicone
cetyl PEG/PPG-7/3 dimethicone
cetyl PEG-8 dimethicone
lauryl isopentyl-PEG/PPG-18/18 methicone
lauryl PEG/PPG-18/18 methicone
lauryl PEG-10 methyl ether dimethicone
lauryl PEG-10 tris(trimethylsiloxy)silylethyl dimethicone
lauryl PEG-8 dimethicone
lauryl PEG-8 PPG-8 dimethicone
lauryl PEG-9 polydimethylsiloxyethyl dimethicone
lauryl polyglyceryl-3 polydimethylsiloxyethyl dimethicone
methoxy PEG-11 methoxy PPG-24 dimethicone
methoxy PEG/PPG-25/4 dimethicone
methoxy PEG-13 ethyl polysilsesquioxane
PEG/PPG-10/2 dimethicone
PEG/PPG-10/3 oleyl ether dimethicone
PEG/PPG-12/16 dimethicone
PEG/PPG-12/18 dimethicone
PEG/PPG-14/4 dimethicone
PEG/PPG-15/15 dimethicone
PEG/PPG-15/5 dimethicone
PEG/PPG-16/2 dimethicone
PEG/PPG-16/8 dimethicone
PEG/PPG-8/14 dimethicone
PEG/PPG-8/26 dimethicone
PEG-10 dimethicone
PEG-10 methyl ether dimethicone
PEG-10 polydimethylsiloxyethyl dimethicone/bis-vinyl dimethicone crosspolymer
PEG-11 methyl ether dimethicone
PEG-12 dimethicone
PEG-14 dimethicone
PEG-17 dimethicone
PEG-3 dimethicone
PEG-32 methyl ether dimethicone
PEG-4 PEG-12 dimethicone
PEG-6 dimethicone
PEG-6 methyl ether dimethicone
PEG-7 dimethicone
PEG-7 methyl ether dimethicone
PEG-8 cetyl dimethicone
PEG-8 dimethicone
PEG-8 dimethicone dimer dilinoleate
PEG-8 dimethicone/dimer dilinoleic acid copolymer
PEG-8 methicone
PEG-8 methyl ether dimethicone
PEG-8 PEG-4 dimethicone
PEG-8 PPG-8 imethicone
PEG-9 dimethicone

PEG-9 methyl ether dimethicone
PPG-25 dimethicone
PEG-9 polydimethylsiloxyethyl dimethicone
polysilicone-13
PPG-12 butyl ether dimethicone
PPG-12 dimethicone
PPG-27 dimethicone
PPG-4 oleth-10 dimethicone
PPG-2 dimethicone
stearoxy dimethicone
Ssearoxymethicone/dimethicone copolymer

These ingredients are reported to function as hair conditioning agents, viscosity increasing agents, emulsion stabilizers, and film formers. The highest reported concentrations of use were 14% PEG/PPG-17/18 dimethicone in perfumes, 12% bis-hydroxyethoxypropyl dimethicone in blushes, and 10.7% PEG/PPG-19/19 dimethicone in eye products.

Citrus-Derived Ingredients

The Panel tabled further discussion of 198 citrus-derived ingredients to allow CIR staff to reorganize the report and to obtain clarification from the Research Institute for Fragrance Materials (RIFM) on the functions of some of the ingredients. These ingredients were presented in a single safety assessment report addressing ingredients from all of the citrus plant species currently reported to be used in cosmetics in the *International Cosmetic Ingredient Dictionary and Handbook*. The Panel felt revising this report into smaller subgroups would be a manageable and meaningful alternative approach to assessing the safety of these ingredients.

The Panel recommended that CIR sort the ingredients by the plant parts from which they are derived, starting with the parts reported to have the greatest number of uses in the FDA's VCRP. For example, citrus limon (lemon) peel oil has the most reported uses, so the first assessment reviewed by the Panel will focus on all citrus-derived peel oils. If this approach works well, or if most, if not all, of the peel oil ingredients are used solely as fragrance ingredients (which are reviewed by RIFM), then the next ingredient group to be reviewed will be citrus-derived fruit extracts, because citrus limon (lemon) fruit extract has the second greatest number of overall reported uses.

Methylisothiazolinone

The Panel tabled their discussion on methylisothiazolinone (MI) to allow a QRA to be performed using corrected EC_3 (i.e., the effective concentrations of the test substance required to produce a three-fold increase in the stimulation index compared to vehicle-treated controls) from a local lymph node assay (LLNA) that the Panel had previously considered when this ingredient was reviewed in 2008. While QRA may be available in the near future from Cosmetics Europe, the Panel strongly recommended that a QRA be performed in the United States in a timely manner to ensure that the Panel can evaluate this ingredient at the June 2014 meeting.

2015 **Priorities**

The draft of the 2015 Priority list was given to the Panel. There are 22 reports on the list, however it is likely that not all of those listed will be chosen for work in 2015.

- yeast extract – 583 uses
- polysilicone-2 – 515 uses
- sea salt – 498 uses
- phosphoric acid – 443 uses
- dicalcium phosphate – 353 uses
- magnesium carbonate – 429 uses
- tridecyl trimellitate – 426 uses
- stearalkonium bentonite – 403 uses
- HDI/trimethylol hexyllactone crosspolymer – 388 uses
- ammonium acryloyldimethyltaurate/VP copolymer – 383 uses
- hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer – 383 uses
- panthenyl ethyl ether – 375 uses
- adipic acid/neopentyl glycol/trimellitic anhydride copolymer – 367 uses
- tetrahexyldecyl ascorbate – 365 uses
- polyglyceryl-3 diisostearate – 358 uses
- 2-oleamido-1,3-octadecanediol – 352 uses
- etidronic acid – 345 uses
- helianthus annuus (sunflower) seed extract – 344 uses
- rosa canina fruit extract – 343 uses
- sodium methyl cocoyl taurate – 335 uses
- glycine soja (soybean) protein [recited in the VCRP as: glycine max (soybean) protein] – 329 uses
- tetradecene – 327 uses

The list is based on use data from FDA's VCRP, received from FDA in March 2014. These 2015 CIR priorities are based on those ingredients listed in the 2014 VCRP database that have not been reviewed by CIR and have the largest number of uses. Some ingredients are excluded from review by the CIR, as discussed in the CIR Procedures. This list only names the lead ingredients. Families of ingredients may be reviewed, as appropriate. Interested parties are invited to comment on the ingredients listed, including comments on the ingredients that might be included in each ingredient family. Proposed ingredient families may be found, starting at page 50, at the following url http://www.cir-safety.org/sites/default/files/w2-online.pdf

CIR plans to finalize the proposed 2015 priority list at the June meeting.

Scientific Literature Reviews

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

  ceramides
  avena sativa (oat)-derived ingredients
  alkyl phosphates
  styrene and vinyl-type styrene copolymers
  2-amino-3-hydroxypyridine

  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 June 9-10, 2014.

- **These literature reviews are currently in preparation**

  polyene group
  inorganic hydroxides
  glycerin
  sodium benzotriazolyl butylphenol sulfonate
  PEGylated alkyl glycerides
  plant polysaccharide gums
  Centella asiatica-derived ingredients

Re-reviews for the next Panel meeting

- **Polyvinyl Alcohol**

  The Panel tabled approval of the summary of its action at the December 2013 meeting at which it was determined not to reopen the safety assessment of polyvinyl alcohol. The Panel would like to review the original report, as well as the re-review document that was presented in 2013, to determine if the data adequately support the safety of increased use concentrations in leave-on products.

Next CIR Expert Panel Meeting

Monday and Tuesday, June 9-10, 2014 at the Washington Court Hotel, 525 New Jersey Avenue, NW, Washington, DC 20001 --- Please contact Carla Jackson (jacksonc@cir-safety.org) at CIR before the meeting if you plan to attend.