Announcement

Cosmetic Ingredient Review Expert Panel
127th Meeting (June 10-11, 2013) - Findings

June 14, 2013

● **Final Safety Assessments**
- **Animal- and plant-derived amino acids – 21 ingredients**
- **Boron nitride – 1 ingredient**
- ***Hypericum perforatum*-derived ingredients – 7 ingredients**
- **Nitrocellulose and collodion – 2 ingredients**

● **Tentative Safety Assessments**
- ***Achillea millefolium*-derived ingredients – 3 ingredients**
- **Alkyl PEG/PPG Ethers – 131 ingredients**
- **Alumina and aluminum hydroxide – 2 ingredients**
- **Dialkyl sulfosuccinate salts – 8 ingredients**
- **Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl – 1 ingredient**
- **Isethionate salts – 12 ingredients**
- **Methyl glucose polyethers & esters – 25 ingredients**
- **Polyquaternium-22 and polyquaternium-39 – 2 ingredients**
- **Tromethamine – 3 ingredients**

● **Insufficient Data Announcements**
- **Amino acid alkyl amides – 115 ingredients**
- **Chamomile-derived ingredients – 14 ingredients**

● **Re-review and New Data**
- **Formaldehyde and methylene glycol – not reopened**
- **PVP – not reopened**
- **Retinol and retinyl palmitate – not reopened**
- **Re-review summaries for HC yellow no. 4 and HC orange no. 1 – approved**

● **127th Meeting Notes**
- **Director's report**
- **2014 ingredient review priorities**
- **Scientific literature reviews posted on the CIR website**
- **Re-reviews for the next Panel meeting**
- **Scientific Literature Reviews under development**
- **Next CIR Expert Panel Meeting – Monday and Tuesday, September 9-10, 2013**

Final Safety Assessments

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. Unpublished data cited as references in CIR safety assessments are available for review. Final safety assessments and final amended safety assessments will be posted on the CIR website at www.cir-safety.org.

Animal- and plant-derived amino acids

The 21 animal- and plant-derived amino acids ingredients listed below are safe in the present practices of use and concentration as described in the safety assessment.

apricot kernel amino acids*
collagen amino acids
corn gluten amino acids*
elastin amino acids*
garcinia mangostana amino acids*
hair keratin amino acids
jojoba amino acids*
keratin amino acids
lupine amino acids
lycium barbarum amino acids*
milk amino acids
oat amino acids
rice amino acids
sesame amino acids*
silk amino acids
soy amino acids
spirulina amino acids*
sweet almond amino acids*
vegetable amino acids
wheat amino acids
yeast amino acids*

**Not reported to be in current use. Were ingredients not reported to be 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 animal- and plant-derived amino acids function as skin and hair conditioning agents. The safety of α-amino acids as direct food additives has been well established based on extensive research through acute and chronic dietary exposures. The Panel focused its review on dermal irritation and sensitization data relevant to the use of these ingredients in topical cosmetics and relied on its past findings on the safety of α-amino acids.

The discussion addressed the potential that incomplete enzymatic hydrolysis of the parent proteins may lead to residual di- or tripeptides. Concern was expressed over potential that such small peptides could cause allergic reactions in sensitive individuals. The Panel stated that industry should continue to manufacture plant- and animal-derived amino acids in a way that minimizes residual peptides.

The Panel reiterated that a safety assessment for hydrolyzed protein ingredients from plant and animal sources will be developed on a separate track.

Boron Nitride

Boron nitride is safe in the present practices of use and concentration in cosmetics.

This ingredient is an inorganic compound with a crystalline form that can be hexagonal or cubic, and is reported to function in cosmetics as a slip modifier (i.e., it has a lubricating effect). Boron nitride is a chemically inert and insoluble ingredient, and its crystalline lattice structure makes it a very large molecule that is not expected to penetrate the skin. While the highest reported concentration of use of boron nitride is 25% in eye shadow formulations and sensitization data were only available at a maximum concentration of 18.7% in formulation, boron nitride was not expected to cause sensitization because the stratum corneum would act as an effective barrier.

***Hypericum perforatum*-derived ingredients (amended)**

The 7 ingredients listed below are safe in the present practices of use and concentration in cosmetics.

hypericum perforatum extract
hypericum perforatum flower extract
hypericum perforatum flower/leaf extract*
hypericum perforatum flower/leaf/stem extract
hypericum perforatum flower/twig extract*
hypericum perforatum leaf extract*
hypericum perforatum oil

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

This is an amended safety assessment. One common name for this plant is St. John's wort. These ingredients function in cosmetics as skin-conditioning agents – miscellaneous and antimicrobial agents, but are used at low concentrations. The Panel reviewed relevant animal and human data. Because formulators may use more than one botanical ingredient in a formulation, caution was urged to avoid levels of toxicological and allergenic concern for plant constituents, such as hypericin. The Panel also reiterated that all botanical ingredients can contain pesticide residues and heavy metals as impurities, and that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulations.

Nitrocellulose and collodion

Nitrocellulose and collodion are safe in the present practices of use and concentration in cosmetics.

Nitrocellulose is used almost exclusively in nail products. The maximum reported use concentration of nitrocellulose is 41% in "nail stickers" made of dried nail polish; the maximum reported use concentration in nail polish and enamels is 22%. Collodion is reported to have a maximum concentration of use of 14% in nail polish and enamel. While it appeared that collodion might properly be considered a mixture containing nitrocellulose, collodion is a listed cosmetic ingredient and has reported uses. So, collodion was added to the title of this report. The molecular weight and chemical properties of nitrocellulose suggested little likelihood of significant dermal absorption, and there is little possibility of biotransformation were any penetration to occur.

Tentative Safety Assessments

*These tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before **June 21, 2013**. 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 **August 21, 2013, or sooner if possible.** These reports may be scheduled for review by the CIR Expert Panel at its **September 9-10, 2013** meeting.*

***Achillea millefolium*-derived ingredients**

The Panel issued a tentative safety assessment for public comment with the conclusion that these 3 Achillea millefolium-derived ingredients listed below were safe as cosmetic ingredients in the present practices of use and concentration.

achillea millefolium extract
achillea millefolium flower/leaf/stem extract
achillea millefolium flower extract

These ingredients may function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; and fragrance ingredients. The Panel reviewed relevant animal and human data to determine their safety in cosmetics. Achillea millefolium extract was reported to be used in 135 cosmetic products, including 83 leave-on products up to 0.04% and 47 rinse-off products up to 0.03%. There were no uses reported for achillea millefolium flower extract and achillea millefolium flower/leaf/stem extract, but were they to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to achillea millefolium extract.

The Panel stressed that there may be an accumulation of constituents of toxicological and allergenic concern (e.g., hydroquinone, linalool) when multiple botanical ingredients containing these constituents are used in the same formulation. The Panel also reiterated that all botanical ingredients can contain pesticide residues and heavy metals as impurities, and that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

Alkyl PEG/PPG Ethers

The Panel issued a tentative safety assessment for public comment with the conclusion that the 131 alkyl PEG/PPG ethers listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

PEG-4-PPG-7 C13/C15 alcohol*
PEG/PPG-3/6 dimethyl ether*
PEG/PPG-7/12 dimethyl ether*
PEG/PPG-9/2 dimethyl ether
PEG/PPG-14/7 dimethyl ether
PEG/PPG-17/4 dimethyl ether
PEG/PPG-22/40 dimethyl ether*
PEG/PPG-27/14 dimethyl ether*
PEG/PPG-35/40 dimethyl ether
PEG/PPG-36/41 dimethyl ether
PEG/PPG-50/40 dimethyl ether
PEG/PPG-52/32 dimethyl ether*
PEG/PPG-55/28 dimethyl ether
PEG/PPG-4/2 propylheptyl ether*
PEG/PPG-6/2 propylheptyl ether*
PEG-7/PPG-2 propylheptyl ether*
PEG/PPG-8/2 propylheptyl ether*
PEG/PPG-10/2 propylheptyl ether*
PEG/PPG-14/2 propylheptyl ether*
PEG/PPG-40/2 propylheptyl ether*
PPG-2-ceteareth-9
PPG-4-ceteareth-12*
PPG-10-ceteareth-20*
PPG-1-ceteth-1*
PPG-1-ceteth-5*
PPG-1-ceteth-10*
PPG-1-ceteth-20*
PPG-2-ceteth-1*
PPG-2-ceteth-5*
PPG-2-ceteth-10
PPG-2-ceteth-20*
PPG-4-ceteth-1*
PPG-4-ceteth-5*
PPG-4-ceteth-10*
PPG-4-ceteth-20
PPG-5-ceteth-20
PPG-8-ceteth-1
PPG-8-ceteth-2*
PPG-8-ceteth-5*
PPG-8-ceteth-10
PPG-8-ceteth-20
PPG-2 C9-11 pareth-5*
PPG-2 C9-11 pareth-7*
PPG-2 C9-11 pareth-8*
PPG-2 C9-11 pareth-11*
PPG-2 C12-13 pareth-8
PPG-2 C12-15 pareth-6*
PPG-4 C13-15 pareth-15*
PPG-5 C9-15 pareth-6*
PPG-6 C9-11 pareth-5*
PPG-6 C12-15 pareth-12*
PPG-6 C12-18 pareth-11*
PPG-3 C12-14 sec-pareth-7*
PPG-4 C12-14 sec-pareth-5*
PPG-5 C12-14 sec-pareth-7*
PPG-5 C12-14 sec-pareth-9*
PPG-1-deceth-4*
PPG-1-deceth-5*
PPG-1-deceth-6*
PPG-1-deceth-7*
PPG-2-deceth-3
PPG-2-deceth-5*
PPG-2-deceth-7*
PPG-2-deceth-8*
PPG-2-deceth-10*
PPG-2-deceth-12
PPG-2-deceth-15*
PPG-2-deceth-20*
PPG-2-deceth-30*
PPG-2-deceth-40*
PPG-2-deceth-50*
PPG-2-deceth-60*
PPG-4-deceth-4*
PPG-4-deceth-6*
PPG-6-deceth-4*
PPG-6-deceth-9*
PPG-8-deceth-6*
PPG-14-deceth-6*
PPG-6-decyltetradeceth-12*
PPG-6-decyltetradeceth-20
PPG-6-decyltetradeceth-30
PPG-13-decyltetradeceth-24
PPG-20-decyltetradeceth-10
PPG-9-ethylhexeth-5*
PPG-1-isodeceth-4*
PPG-1-isodeceth-6*
PPG-1-isodeceth-7*
PPG-1-isodeceth-9*
PPG-2-isodeceth-4*
PPG-2-isodeceth-6*
PPG-2-isodeceth-8*
PPG-2-isodeceth-9*
PPG-2-isodeceth-10*
PPG-2-isodeceth-12
PPG-2-isodeceth-18*
PPG-2-isodeceth-25*
PPG-3-isodeceth-1*
PPG-4-isodeceth-10*
PPG-3-isosteareth-9
PPG-2-laureth-5*
PPG-2-laureth-8*
PPG-2-laureth-12*
PPG-3-laureth-8*
PPG-3-laureth-9*
PPG-3-laureth-10*
PPG-3-laureth-12*
PPG-4 laureth-2*
PPG-4 laureth-5*
PPG-4 laureth-7*
PPG-4-laureth-15*
PPG-5-laureth-5
PPG-6-laureth-3*
PPG-25-laureth-25
PPG-3-myreth-3*
PPG-3-myreth-11*
PPG-2-PEG-11 hydrogenated lauryl alcohol ether*
PPG-3-PEG-6 oleyl ether*
PPG-9-steareth-3*
PPG-23-steareth-34*
PPG-30 steareth-4*
PPG-34-steareth-3
PPG-38 steareth-6*
PPG-1 trideceth- 6

PPG-1 trideceth-13*
PPG-4 trideceth-6*
PPG-6 trideceth-8*
propylene glycol capreth-4*
propylene glycol isodeceth-4*
propylene glycol isodeceth-12*
propylene glycol laureth-6*
propylene glycol oleth-5*

**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 maximum reported leave-on use concentrations are up to 10% PPG-5-ceteth-20 in "other" fragrance preparations and in tonics, dressings, and other hair grooming aids and up to 7% PEG/PPG-14/7 dimethyl ether in face and neck, and body and hand products.

These ingredients are similar to the alkyl PEG ether ingredients that have already been reviewed and found safe when formulated to be non-irritating by the CIR Expert Panel. The principle differences between the alkyl PEG ethers and the alkyl PEG/PPG ethers are the polypropylene glycol (PPG) repeat units that are included to fine tune the surfactant properties of these ingredients. Inclusion of the PPGs did not raise any additional safety concerns because the PPGs were reviewed recently by the CIR and found safe when formulated to be non-irritating. While there were few data available on the individual alkyl PEG/PPG ethers, the existing data on the analogues support the safety of this ingredient family. Additionally, concerns, such as the possibility of the presence of the residual starting materials ethylene oxide and propylene oxide or the potential by-product 1,4-dioxane, and the possibility that these ingredients can be penetration enhancers, will be addressed in the safety assessment as done previously in the alkyl PEG ethers report.

Alumina and aluminum hydroxide

The Panel issued a tentative safety assessment for public comment with the conclusion that alumina and aluminum hydroxide are safe in the present practices of use and concentration in cosmetics.

Alumina was reported to be used in 523 leave-on products at concentrations up to 60%, and in 40 rinse-off products at concentrations up to 30%. Aluminum hydroxide was reported to be used in 572 leave-on products at concentrations up to 10.1% and 6 rinse-off products at concentrations up to 8.8%. In addition to published safety data, the Panel relied on the FDA's conclusion of safety for the use of alumina in medical devices (i.e., replacement knees and dental implants). The Panel also considered the FDA's approval of aluminum hydroxide in over-the-counter drugs (i.e., antacids) as well as in colors used in medical devices (i.e., sutures and bone cement).

Because the names of these ingredients may raise a concern that use in cosmetics would involve exposure to aluminum, the Panel directly addressed that concern. Acknowledging the ongoing scientific debate about aluminum's connection to Alzheimer's disease and breast cancer, the Panel suggested that this was not relevant to these ingredients because these two ingredients are not the same as the elemental aluminum and aluminum. Use of alumina and aluminum hydroxide in cosmetics would not result in significant systemic availability of aluminum.

Dialkyl Sulfosuccinate Salts

The Panel issued a tentative amended safety assessment for public comment with the conclusion that the 8 dialkyl sulfosuccinate salts listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

ammonium dinonyl sulfosuccinate*
diamyl sodium sulfosuccinate*
dicapryl sodium sulfosuccinate*
diethylhexyl sodium sulfosuccinate
diheptyl sodium sulfosuccinate*
dihexyl sodium sulfosuccinate*
diisobutyl sodium sulfosuccinate*
ditridecyl sodium sulfosuccinate*

**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 re-opened the safety assessment of diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate; last reviewed in 1998) to add an additional seven dialkyl sulfosuccinate salts, and issued the tentative amended report. The Expert Panel found the existing data on diethylhexyl sodium sulfosuccinate sufficient to evaluate the safety of the other diesters, and issued a tentative amended safety assessment for public comment. Diethylhexyl sodium sulfosuccinate is the only alky sulfosuccinate salt named in this report that is in use, and the greatest maximum reported leave-on use concentration is 4.4% in eyebrow pencil formulations.

The Panel stated that diethylhexyl sodium sulfosuccinate is a reasonable representative of all of the diesters. All of the diesters named above are of a similar alkyl chain length and are symmetrically substituted, and all have similar functions in cosmetic formulations. The re-review document presented to the Panel originally suggested including monoesters in addition to the diesters. However, the Panel did not find that diethylhexyl sodium sulfosuccinate is representative of the polar monoesters, and the data could not be "read-across" to address their safety; therefore, the monoesters are not included in this amended safety assessment.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl

The Panel issued a tentative safety assessment for public comment with the conclusion that this ingredient is safe in the present practices of use and concentration in hair dyes.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was reported to be used in 75 hair dyes and colors at a maximum concentration of 0.28%. Extensive data developed to support the safety of this oxidative hair dye ingredient in Europe was reviewed by the Panel. The Panel noted that UV absorption was seen in the UVC region of the spectrum, but because UVC is not present in sunlight, no photochemical interaction would be seen in routine use. There was a small absorption peak in the UVB range, but the available phototoxicity data demonstrated no adverse reactions.

While the safety of individual hair dye ingredients are not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information. Currently available epidemiology studies provided insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. A detailed summary of the available hair dye epidemiology data is available at http://www.cir-safety.org/cir-findings .

Isethionate salts

The Panel issued a tentative amended safety assessment on isethionate salts with the conclusion that the 12 ingredients listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

sodium cocoyl isethionate
ammonium cocoyl isethionate
sodium hydrogenated cocoyl methyl isethionate*
sodium isethionate
sodium lauroyl isethionate
sodium lauroyl methyl isethionate
sodium methyl isethionate
sodium myristoyl isethionate*
sodium oleoyl isethionate*
sodium oleyl methyl isethionate*
sodium palm kerneloyl isethionate*
sodium stearoyl methyl isethionate*

**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 considered that the available single dose and repeated dose animal studies, including reproductive and developmental toxicity studies, supported the safety of sodium cocoyl isethionate and sodium isethionate. The Panel noted the absence of carcinogenicity data, but considered the data demonstrating that sodium cocoyl isethionate and sodium isethionate were not mutagenic or clastogenic in in vitro genotoxicity studies adequate to support the safety of these ingredients. Although there are data gaps, the similar chemical structures, physicochemical properties, and functions (all are used as surfactants) and concentrations of use in cosmetics allow grouping these ingredients together and extending the available toxicological data to support the safety of the entire group. The Panel noted that most surfactants exhibit some irritancy.

The Panel looked at changes in the pattern and concentration of use since the original safety assessment of sodium cocoyl isethionate. They noted that the most recently reported concentration of use of sodium cocoyl isethionate in rinse-off products is 53%, which is essentially the level previously considered safe.

Methyl Glucose Polyethers and Esters

The Panel issued a revised tentative safety assessment with the conclusion that the 25 methyl glucose polyethers and esters listed below are safe in the present practices of use and concentration in cosmetics.

Esters:
methyl glucose caprylate/caprate*
methyl glucose dioleate
methyl glucose isostearate*
methyl glucose laurate*
methyl glucose sesquicaprylate/ sesquicaprate*
methyl glucose sesquicocoate*
methyl glucose sesquiisostearate
methyl glucose sesquilaurate*
methyl glucose sesquioleate
methyl glucose sesquistearate

Polyethers:
PPG-10 methyl glucose ether
PPG-20 methyl glucose ether
PPG-25 methyl glucose ether*
PPG-20 methyl glucose ether acetate*
PPG-20 methyl glucose ether distearate
methyl gluceth-10
methyl gluceth-20

Esters and polyethers:
PEG-120 methyl glucose dioleate
PEG-20 methyl glucose distearate
PEG-80 methyl glucose laurate*
PEG-20 methyl glucose sesquicaprylate/sesquicaprate*
PEG-20 methyl glucose sesquilaurate*
PEG-20 methyl glucose sesquistearate
PEG-120 methyl glucose triisostearate*
PEG-120 methyl glucose trioleate

**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.*

Ingredients classified as polyethers function as skin and hair conditioning agents, whereas, the methyl glucose esters function only as skin conditioning agents in cosmetic products. This conclusion was previously issued for all but 3 ingredients in this group, for which the available data were insufficient because of inadequate data to support use in lipsticks. Those three ingredients were: methyl glucose sesquistearate, PEG-20 methyl glucose sesquistearate, and PEG-20 methyl glucose distearate.

Lipstick use concentration data were clarified and newly available toxicity data were obtained from the European Chemicals Agency's (ECHA) website and used with permission. Accordingly, the Panel considered that repeated dose toxicity/reproductive and developmental toxicity data on isostearic acid, esters with methyl α-D-glucoside, from the ECHA website, support the safety of the three ingredients as used in lipsticks. While no use concentrations were available on PEG-20 methyl glucose sesquistearate in lipsticks, it was assumed that this ingredient is being used at concentrations no greater than the 1% maximum reported for methyl glucose sesquistearate.

Polyquaternium-22 and polyquaternium-39

The CIR Expert Panel issued a tentative safety assessment for public comment with the conclusion that Polyquaternium-22 and polyquaternium-39 are safe in the present practices of use and concentration in cosmetics.

Both ingredients function as antistatic agents, film formers, and hair fixatives in cosmetic products, and polyquaternium-22 and polyquaternium-39 are used at concentrations up to 2% and 3%, respectively. Relevant residual monomer data on polyquaternium,-22 and polyquaternium-39 were provided, and the unreacted monomers content was considered to be below the levels of toxicological concern. For example, acrylic acid (< 50 ppm or < 1000 ppm) and dimethyldiallyl ammonium chloride (<1% or < 2%) monomers used to manufacture both polymers were detected at low levels. For polyquaternium-39, where acrylamide monomer is used in the manufacturing, residual levels of acrylamide were below the level of detection (< 1 ppm).

The Panel acknowledged that there were data gaps for both ingredients, including no available skin sensitization data on polyquaternium-22. However, it was agreed that these polymers are large, highly polar molecules that would not penetrate the skin. Furthermore, though dermal absorption is not likely, the Panel noted that concern over skin irritation/sensitization potential is not warranted based on the negative skin irritation data on polyquaternium -22 and polyquaternium-39, and the negative skin sensitization data on polyquaternium-39.

Tromethamine

The CIR Expert Panel issued a tentative safety assessment for public comment with the conclusion that tromethamine, aminomethyl propanediol (AMPD) and aminoethyl propanediol (AEPD) are safe in the present practices of use and concentration in cosmetics.

These ingredients are aliphatic or substituted aliphatic compounds. They function in cosmetics as fragrance ingredients and pH adjusters. The Panel reviewed relevant animal and human safety test data related to these ingredients. In particular, impurities in these ingredients are below the levels of toxicological concern. The similar structure, properties, functions and uses of these ingredients enabled grouping them and using the available toxicological data to assess the safety of the entire group. Tromethamine is used in 488 leave-on products and 70 rinse-off products at concentrations up to 3.7%. AMPD was reported by the VCRP to be used in 131 leave-on products and 2 rinse-off products at concentrations up to 7%. There were no reported uses for AEPD. Were AEPD to be used in the future, it is expected that it would be used in product categories and at concentrations comparable to others in this group.

Since these ingredients are primary amines, not secondary amines, formation of nitrosating compounds was not a concern.

Insufficient Data Announcements

For these insufficient data announcements, interested persons are given an opportunity to comment, provide information and/or request an oral hearing before the CIR Expert Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, and are available for review by any interested party. Please submit data and/or comments to CIR by ***August 14, 2013****, or sooner if possible. This report is scheduled for review by the CIR Expert Panel at its* ***September 9-10, 2013*** *meeting.*

Amino Acid Alkyl Amides

The Expert Panel requested additional data to support the safety of 115 amino acid alkyl amides.

The additional data needed are (1) dermal irritation and sensitization data for lauroyl lysine at the highest use concentration reported (45%) and (2) dermal irritation and sensitization data for sodium lauroyl glutamate at the highest use concentration reported (40%). These data, if made available, will span the chemistry space for this group. It was also noted that any available data on disodium malyl tyrosinate would be useful.

The 115 ingredients in this safety assessment are listed below.

acetyl arginine
acetyl cysteine
acetyl glutamic acid
acetyl glutamine
acetyl histidine
acetyl methionine
acetyl proline
acetyl tyrosine
capryloyl collagen amino acids
capryloyl glycine
capryloyl gold of pleasure amino acids
capryloyl keratin amino acids
capryloyl pea amino acids
capryloyl quinoa amino acids
capryloyl silk amino acids
cocoyl glutamic acid
dipalmitoyl cystine
dipotassium capryloyl glutamate
dipotassium undecylenoyl glutamate
disodium capryloyl glutamate
disodium cocoyl glutamate
disodium hydrogenated tallow glutamate
disodium N-lauroyl aspartate
disodium lauroyl glutamate
disodium malyl tyrosinate
disodium stearoyl glutamate
disodium undecylenoyl glutamate
lauroyl arginine
lauroyl collagen amino acids
lauroyl glutamic acid
lauroyl lysine
lauroyl proline
lauroyl silk amino acids
magnesium palmitoyl glutamate
myristoyl glutamic acid
oleoyl tyrosine
palmitoyl alanine
palmitoyl arginine
palmitoyl collagen amino acids
palmitoyl glutamic acid
palmitoyl glycine
palmitoyl gold of pleasure amino acids
palmitoyl isoleucine
palmitoyl keratin amino acids
palmitoyl millet amino acids
palmitoyl oat amino acids
palmitoyl pea amino acids
palmitoyl proline
palmitoyl quinoa amino acids
palmitoyl silk amino acids
potassium caproyl tyrosine
potassium capryloyl glutamate
potassium cocoyl glutamate
potassium cocoyl glycinate
potassium cocoyl rice amino acids
potassium lauroyl collagen amino acids
potassium lauroyl glutamate
potassium lauroyl oat amino acids
potassium lauroyl pea amino acids
potassium lauroyl silk amino acids
potassium lauroyl wheat amino acids
potassium myristoyl glutamate
potassium olivoyl/lauroyl wheat amino acids
potassium stearoyl glutamate
potassium undecylenoyl glutamate
propionyl collagen amino acids
sodium caproyl prolineate
sodium capryloyl glutamate
sodium cocoyl alaninate
sodium cocoyl amino acids
sodium cocoyl apple amino acids
sodium cocoyl barley amino acids
sodium cocoyl collagen amino acids
sodium cocoyl glutamate
sodium cocoyl glutaminate
sodium cocoyl glycinate
sodium cocoyl/hydrogenated tallow glutamate
sodium cocoyl oat amino acids
sodium cocoyl/palmoyl/sunfloweroyl glutamate
sodium cocoyl proline
sodium cocoyl threoninate
sodium cocoyl wheat amino acids
sodium hydrogenated tallowoyl glutamate
sodium lauroyl aspartate
sodium lauroyl collagen amino acids
sodium lauroyl glutamate
sodium lauroyl millet amino acids
sodium lauroyl/myristoyl aspartate
sodium lauroyl oat amino acids
sodium lauroyl silk amino acids
sodium lauroyl wheat amino acids
sodium myristoyl glutamate
sodium olivoyl glutamate
sodium palmitoyl proline
sodium palmoyl glutamate
sodium stearoyl glutamate
sodium/TEA-lauroyl collagen amino acids
sodium/TEA-lauroyl keratin amino acids
sodium/TEA-undecylenoyl collagen amino acids
sodium undecylenoyl glutamate
stearoyl glutamic acid
stearoyl leucine
TEA-cocoyl alaninate
TEA-cocoyl glutamate
TEA-cocoyl glutaminate
TEA-hydrogenated tallowoyl glutamate
TEA-lauroyl collagen amino acids
TEA-lauroyl glutamate
TEA-lauroyl keratin amino acids
TEA-lauroyl/myristoyl aspartate
undecylenoyl collagen amino acids
undecylenoyl glycine
undecylenoyl phenylalanine
undecylenoyl wheat amino acids
zinc lauroyl aspartate

Chamomile Ingredients

The Panel determined that there are sufficient differences in composition between chamomile ingredients from *Chamomilla recutita* (so-called German Chamomile) and *Anthemis nobilis*, (so-called Roman Chamomile) to split these into two reports.

One report will address *Chamomilla recutita*-derived ingredients and the other will address *Anthemis nobilis*-derived ingredients. These are presented separately below.

***Chamomilla recutita*-derived ingredients**

The available data are insufficient for evaluating the safety of this group of ingredients in cosmetic products. The following data are needed:

(1) Skin irritation and sensitization data on chamomilla recutita (matricaria) flower extract at current use concentrations.

The group includes:

chamomilla recutita (matricaria) extract,
chamomilla recutita (matricaria) flower,
chamomilla recutita (matricaria) flower extract,*
chamomilla recutita (matricaria) flower/leaf extract,
chamomilla recutita (matricaria) flower/leaf/stem extract,
chamomilla recutita (matricaria) flower/leaf/stem water,
chamomilla recutita (matricaria) flower powder,
chamomilla recutita (matricaria) flower water,
chamomilla recutita (matricaria) leaf extract, and
chamomilla recutita (matricaria) oil.

The Panel also agreed that data from the final CIR safety assessments on bisabolol and azulene, which are both components constituents of chamomilla recutita (matricaria) flower oil, might be useful for assessing the safety of chamomilla recutita (matricaria) flower oil and should be incorporated into this safety assessment. Additionally, β-farnesene, linalool and quercetin, are constituents of *Chamomilla recutita*, and the safety assessment should address these constituents. The Panel noted that the pesticides and heavy metals content should be below levels of toxicological concern, independent of species.

***Anthemis nobilis*-derived ingredients**

The available data are insufficient for evaluating the safety of this group of ingredients in cosmetic products. The following data are needed:

(1) Composition data on all anthemis nobilis ingredients, except anthemis nobilis flower oil, and
(2) Skin irritation and sensitization data on all anthemis nobilis ingredients, except anthemis nobilis flower oil, at current use concentrations.

The group includes:

anthemis nobilis flower extract,*
anthemis nobilis flower oil,
anthemis nobilis flower powder,* and
anthemis nobilis flower water.*

The Panel noted that the pesticides and heavy metals content should be below levels of toxicological concern, independent of species.

Re-review and New Data

Formaldehyde and Methylene Glycol

The Panel reaffirmed that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin† concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products. However, formaldehyde and methylene glycol are unsafe in the present practices of use and concentration in hair smoothing products (a.k.a. hair straightening products).

†Formalin is an aqueous solution wherein formaldehyde (gas) has been added to water to a saturation point, which is typically 37% formaldehyde (w/w). Because of the equilibrium between formaldehyde and methylene glycol in aqueous solution, formalin is composed of both formaldehyde and methylene glycol.

Dr. Robert Golden, President, ToxLogic, briefed the Panel on behalf of the Professional Keratin Smoothing Council (PKSC). Dr. Golden explained the PKSC position that methylene glycol is not chemically or toxicologically equivalent to formaldehyde and that the term "formaldehyde equivalents" is not appropriate. Additionally, they proposed establishing a limit of 3% methylene glycol in keratin smoothing products. Further, they recommended attaching a warning label, and restricting use to licensed professionals with additional training and certification on the safe use of such products and the ventilation issues. They asserted that proper product application and drying procedures (e.g., using a fine-tooth comb to remove excess product before heating the hair, and using cooler blow-dryer temperature settings), ventilation, and attention to avoiding sensory irritation can ensure that exposures do not exceed OSHA standards and American Conference of Government Industrial Hygienists (ACGIH) recommendations for occupational exposures to formaldehyde.

The Panel did not accept the rationale that Dr. Golden and the PKSC offered against using the term "formaldehyde equivalents," as defined in CIR's safety assessment report. The Panel remains convinced that this term best captures the idea that methylene glycol is rapidly, reversibly and continuously converted to formaldehyde, and vice versa, even at equilibrium, which can be easily shifted by heating, drying, and other conditions to increase the amount of formaldehyde. The concept of "formaldehyde equivalents," as defined, is also consistent with what is known about the interactions of exogenous formaldehyde with the tissues of the nasal passages and elsewhere in the respiratory tract. Further, this concept conforms to the analytical methods used by OSHA and other regulatory agencies to monitor formaldehyde concentrations in the air, the results of which are directly and meaningfully comparable to the pertinent regulatory standards and guidelines.

The Panel reiterated its position that, in principle, measures such as limiting the concentrations of formaldehyde and methylene glycol in hair smoothing products, controlling the amount of product applied, using lower drying temperatures, and specifying approaches for adequate ventilation could help ensure that these products would be used safely in the future. However, the information provided by Dr. Golden and the PKSC did not include new exposure data with products at the proposed lower use concentration of 3% methylene glycol. Further, the information provided did not explain how the distribution and use of hair smoothing products could be effectively restricted or controlled, how the recommended training program would be implemented, or how the recommended measures, overall, would affect release of gaseous formaldehyde and exposures to salon workers and their customers.

The Panel is amenable to receiving new data characterizing exposures that would result from using keratin smoothing products containing methylene glycol and formaldehyde in accordance with the proposed measures. However, the Panel emphasized that any new information should focus specifically on addressing use and exposure issues, including both the elaboration of exposure-reduction/prevention strategies and the characterization of likely exposures. The Panel also emphasized that their concerns are not limited to the potential for eye and respiratory tract exposures to formaldehyde; the potential for adverse effects from direct dermal exposures during the use of keratin hair smoothing products needs to be addressed as well.

PVP

The Panel reaffirmed the original conclusion that PVP (polyvinylpyrrolidone) is safe in the present practices of use and concentration in cosmetics.

The Panel did note that the original report included extensive data for PVP-iodine and that PVP-iodine is listed in the International Cosmetic Ingredient Dictionary and Handbook as a cosmetic ingredient. There are currently no reported uses of PVP-iodine in cosmetics and, while listed as a cosmetic ingredient, PVP-iodine is actually an approved drug used as an active ingredient in such antiseptics as Betadine. Therefore, the Panel determined to not add PVP-iodine to this safety assessment.

Retinol, Retinoic Acid, and Retinyl Esters

The Expert Panel decided that the published CIR final safety assessment on retinol and retinyl palmitate should not be reopened at this time, but that the progress of a new, ongoing National Toxicology Program (NTP) photococarcinogenesis study on retinyl palmitate and retinoic acid should be monitored.

This decision was made after reviewing the original NTP photococarcinogenesis study on retinol and retinyl palmitate, including the summary of peer review comments and the conclusions presented in the NTP report that was finalized in 2012. The CIR Expert Panel concluded that the results of the original study are ambiguous and very difficult to interpret. The Panel was informed that the NTP has initiated a second photococarcinogenesis study to attempt to address the flaws of the original study, and that a 90-day range-finding study using a vehicle formulation different from that used in the original study has been completed.

In addition, the Panel reviewed toxicity data on retinol and retinyl palmitate published since the final CIR safety assessment was issued, and additional data on retinoic acid, retinyl acetate, and retinyl propionate. However, toxicity data on the following retinyl esters that were of interest were not found in the published literature: retinyl linoleate, retinyl oleate, retinyl rice branate, retinyl soyate, and retinyl tallate. The Panel noted that if a decision is made to reopen the CIR final safety assessment in the future, based on the results of the new NTP photococarcinogenesis study or other new data, retinoic acid should not be included because it is widely used as an FDA-approved drug. However, the Panel indicated that pertinent data on retinoic acid may be retained in the safety assessment, as appropriate. The possibility of adding other retinyl esters to this group remains open. The Panel also expressed interest in reviewing data on residual levels of retinyl palmitate and retinol in the epidermis following the application of these ingredients in the presence of UV light.

Re-review Summaries

The Panel approved the summaries of their actions at the March meeting to not reopen the safety assessments of HC yellow no. 4 and HC orange no. 1, with the addition to the latter of a reference to the Scientific Committee on Consumer Safety (SCCS) Opinion on HC orange no. 1.

127th Meeting Notes

Director's Report

Dr. Andersen introduced Dr. Beth Lange, Mary Kay, the new chair of the Council's CIR Science and Support Committee and welcomed her ongoing participation with the Panel.

He described the safety assessments included in the most recent issue of the *International Journal of Toxicology* and noted that the interval between completion of reports by the Panel and their appearance in the Journal was decreasing significantly. He reviewed the ongoing efforts of Dr. Ivan Boyer, CIR's senior toxicologist, along with Dr. Bart Heldreth, CIR chemist, to develop alternative methods for assessing potential toxicity of cosmetic ingredients. Building on the presentation by EPA's Dr. Ann Richards on her program's efforts in computational toxicology, CIR has expanded the thinking about possible collaboration to include both FDA and CIR interacting with the EPA program.

Dr. Andersen thanked the Panel for participating in the celebration of his career at CIR. He echoed the oft-stated observation that the work of the Panel exceeds the sum of its parts. He explained that the extraordinary efforts of the industry trade association some 37 years ago to establish an independent safety review group and the unwavering commitment to the program over the intervening years, along with all the individuals that make up the CIR Expert Panel and the CIR staff, made his 20 years in the job a real pleasure. This was the final meeting for Dr. Andersen, who is retiring. CIR Deputy Director, Dr. Lillian Gill will move into the Director position in July.

2014 Ingredient Review Priorities

The Panel approved a list of 4 individual ingredients and 11 ingredient groups for review in 2014. The number of ingredients that potentially would be included in each group is given following the title that CIR intends to use to describe the group. The group size can be modified based on available data and the decisions by the Panel.

1. Glycerin
2. Inorganic Hydroxides – 6 ingredients
3. Alga-derived ingredients – 174 ingredients*
4. Ginkgo-derived ingredients – 9 ingredients
5. Phosphoglycerides – 5 ingredients
6. Sodium benzotriazolyl butylphenol sulfonate
7. Styrene and Vinyl-type Styrene Copolymers – 35 ingredients
8. PEGylated Alkyl Glycerides – 53 ingredients
9. *Avena sativa*-derived ingredients – 19 ingredients
10. Centella Asiatica-derived ingredients – 9 ingredients
11. PEG-150 pentaerythrityl tetrastearate
12. Alkoxy Polysiloxanes – 112 ingredients
13. Pyrus malus-derived ingredients – 19 ingredients

14. Potassium Alkyl Phosphates – 21 ingredients
15. 2-Amino-3hydroxypyridine

**The Panel agreed this group was a 2014 review priority, but suggested that initial efforts be put toward better understanding the constituents of the different alga species.*

The Panel also discussed upcoming re-reviews of CIR safety assessments and whether it would be appropriate to modify the time interval at which a re-review is triggered. Currently that interval is 15 years and the possibility of extending that to 20 years was considered. The Panel did not support such an extension of the time interval because such an approach would only move the workload further into the future. Noting that many re-reviews are performed before the 15-year interval based on the need to consider new data that are highly public, the Panel suggested that CIR develop a targeted approach that would identify previous safety assessments that need to be re-reviewed based on information in the scientific literature and other relevant sites.

Scientific Literature Reviews

- **These literature reviews are currently posted on the CIR website at http://www.cir-safety.org/ingredients/glossary/all**
  - alkyl betaines
  - phytosterols
  - *Rosemarinus officinalis* (rosemary)-derived ingredients

Draft reports for these ingredients, along with any unpublished data submitted by interested parties may be presented to the Panel at its meeting on September 9-10, 2013.

In addition, a re-review of the safety assessment listed below may be considered at the September 2013 meeting:
- iodopropynyl butylcarbamate

- **These literature reviews are currently in preparation**
  - *Camellia sinensis*-derived ingredients
  - citrus-derived ingredients
  - hydrogenated polydecenes
  - inorganic sulfates
  - pentaerythrityl tetra-di-t-butyl hydroxyhydrocinnamate
  - plant polysaccharide gums (maltodextrin, etc.)
  - mono- and disaccharides

Next CIR Expert Panel Meeting - Monday and Tuesday, September 9-10, 2013 at the Madison Hotel, 1177 Fifteenth Street, NW, Washington, DC 20005 --- Please contact Carla Jackson (jacksonc@cir-safety.org) at CIR before the meeting if you plan to attend.