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# Announcement

## Cosmetic Ingredient Review Expert Panel 136<sup>th</sup> Meeting (September 21-22, 2015) - Findings

September 25, 2015

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  - Soy Proteins and Peptides – 6 ingredients
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### Final Safety Assessments

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 Unpublished data cited as references in CIR safety assessments are available for review.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

#### Polysaccharide Gums

The Panel issued a final report with the conclusion that the following 105 polysaccharide gums are safe in the present practices of use and concentration, and that the available data are insufficient for determining the safe use of hydrolyzed carrageenan in cosmetic products.

#### *Linear Polysaccharides and Salts Thereof*

agar  
agarose  
algin  
alginic acid  
ammonium alginate\*  
amylose\*

astragalus gummifer gum  
calcium alginate  
calcium carrageenan\*  
carrageenan  
magnesium alginate\*  
mannan

polianthes tuberosa  
polysaccharide  
potassium alginate  
potassium carrageenan\*  
sodium carrageenan  
TEA-alginate\*

### ***Linear – Modified***

amylopectin  
hydrolyzed furcellaran\*  
maltodextrin

potassium undecylenoyl carrageenan\*  
sodium algin sulfate\*

### ***Branched/Unmodified***

amylopectin\*  
aphanothece sacrum  
polysaccharide\*  
arabinoxylan\*  
avena sativa (oat) starch  
cassia angustifolia seed  
polysaccharide  
cichorium intybus (chicory)  
root oligosaccharides  
triticum vulgare(wheat) starch

galactoarabinan  
ghatti gum  
glucomannan  
inulin  
pectin  
phaseolus angularis seed starch\*  
phaseolus radiatus seed starch\*  
pisum sativum (pea) starch\*  
pueraria lobata starch

solanum tuberosum (potato)  
starch  
starch acetate  
sterculia urens gum  
tamarindus indica seed gum  
tapioca starch

### ***Branched – Modified***

calcium starch  
isododecenylsuccinate\*  
calcium starch  
octenylsuccinate\*  
corn starch modified  
dextrin  
dextrin behenate\*  
dextrin isostearate\*  
dextrin laurate\*  
dextrin myristate  
dextrin palmitate  
dextrin  
palmitate/ethylhexanoate  
dextrin stearate  
glyceryl alginate  
glyceryl dimaltodextrin\*  
glyceryl starch  
hydrolyzed pectin  
hydroxypropyltrimonium  
hydrolyzed corn starch

hydroxypropyltrimonium  
hydrolyzed wheat starch  
hydroxypropyl oxidized starch\*  
hydroxypropyl starch  
hydroxypropyltrimonium  
maltodextrin crosspolymer  
laurdimonium hydroxypropyl  
hydrolyzed wheat starch  
palmitoyl inulin\*  
potassium dextrin  
octenylsuccinate\*  
potassium undecylenoyl  
alginate\*  
potato starch modified  
propylene glycol alginate  
sodium carboxymethyl inulin\*  
sodium carboxymethyl starch  
sodium dextrin  
octenylsuccinate  
undecylenoyl inulin\*

sodium hydrolyzed potato  
starch dodecenylsuccinate  
sodium hydroxypropyl  
oxidized starch succinate\*  
sodium oxidized starch  
acetate/succinate  
sodium starch octenylsuccinate  
sodium/TEA-undecylenoyl  
alginate\*  
sodium/TEA-undecylenoyl carrageenan\*  
starch acetate/adipate\*  
starch diethylaminoethyl ether  
starch hydroxypropyltrimonium  
chloride  
starch laurate\*  
starch tallowate\*  
stearoyl inulin  
tapioca starch crosspolymer \*  
TEA-dextrin octenylsuccinate\*

### ***Cyclic***

cyclodextrin  
cyclotetraglucose\*

### ***Cyclic – Modified***

hydroxyethyl cyclodextrin  
hydroxypropyl cyclodextrin  
cyclodextrin hydroxypropyltrimonium chloride\*

cyclodextrin laurate  
methyl cyclodextrin

### ***Unknown Structural Configuration***

algae exopolysaccharides\*  
cassia angustifolia seed polysaccharide\*  
prunus persica (peach) gum\*

### **Unknown Structural Configuration – Modified**

hydrogenated potato starch\*  
hydrogenated starch hydrolysate  
hydrolyzed corn starch hydroxyethyl ether\*  
hydrolyzed corn starch octenylsuccinate

hydrolyzed soy starch\*  
hydrolyzed starch  
hydrolyzed triticum spelta starch\*  
hydrolyzed wheat starch

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

The Panel discussed a study suggesting the induction of colon tumors in rats that received degraded carrageenan (poligeenan) in the diet or in drinking water and determined that the maximum use concentration of polysaccharide gums in lipstick products is low and the burden to the colon that could result from the incidental ingestion of degraded carrageenan in lipstick would be substantially below the no observed effect level (NOEL) for colon carcinogenicity. The Panel encouraged the industry to submit data to clarify the compositions of hydrolyzed carrageenan and degraded carrageenan.

Additional data indicating that the inhalation of konjac flour induced respiratory sensitization in test animals was received, which specifically addressed the extent to which the pulmonary hypersensitivity could be attributed to glucomannan, rather than to some other component of the flour. This data show that the purified antigen named AG40D-2 (acidic protein) was responsible for the observed respiratory sensitization. Thus, concerns about the respiratory sensitization potential of glucomannan were resolved.

The Panel noted the possibility that pesticide residues and heavy metals may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities. The Panel also agreed that the cosmetics industry should be vigilant with respect to minimizing the presence of alkylating and other agents (e.g., haloethylaminopropionic acid; 3-(dodecyl)-2,5-furandione; and 2,3-epoxypropyltrimethylammonium chloride) that are used to modify polysaccharide gums. Recognizing the absence of sensitizing components from polysaccharide gums, the Panel noted that the statement relating to botanicals and sensitizing constituents of concern should be removed from the report abstract and discussion.

### **Soy Proteins and Peptides**

The Panel issued a final safety assessment with the conclusion that the 6 soy-based ingredients listed below are safe in cosmetics in the present practices of use and concentration:

glycine max (soybean) polypeptide  
glycine soja (soybean) peptide\*  
glycine soja (soybean) protein

hydrolyzed soy protein  
hydrolyzed soy protein extract\*  
hydrolyzed soymilk protein

\*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 soy proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. However, the Panel was not concerned that such reactions would be induced by dermal exposure, because these ingredients are water soluble, would not penetrate the skin, and have molecular weights that are well below that which would cause IgE-cross-linking. The Panel reviewed studies showing little-to-no irritation in ocular animal studies, no dermal irritation or sensitization in animals and human subjects, and no reported cases of Type I immediate hypersensitivity reactions from cosmetic use, which support their conclusion for these ingredients.

### **Trialkyl Trimellitates**

The Panel issued a final report with the conclusion that the following 5 trialkyl trimellitates are safe as used in cosmetics when formulated to be non-irritating:

tridecyl trimellitate  
tricaprylyl/capryl trimellitate\*  
triethylhexyl trimellitate  
triisodecyl trimellitate  
triisotridecyl trimellitate

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

The Panel noted the negative results of a phototoxicity study of a lipstick formulation containing 22.3% tridecyl trimellitate. Although there were little data available for triisodecyl trimellitate, information from a published study on triethylhexyl trimellitate, which is a similar ingredient of a smaller molecular weight, indicated no systemic availability of triethylhexyl trimellitate by dermal absorption. Accordingly, triisodecyl trimellitate is not likely to be absorbed, and therefore there was little concern about the safety of this ingredient as used in cosmetics.

## **Tentative Safety Assessments**

Tentative and tentative amended safety assessments will be posted on the CIR website at [www.cir-safety.org](http://www.cir-safety.org) on or before **September 25, 2015**. 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 **November 25, 2015, or sooner if possible**. These reports may be scheduled for review by the CIR Expert Panel at its **December 14-15, 2015** meeting.

### Alkonium Clays

The Panel issued a tentative report for public comment with the conclusion that the available data or information are insufficient to make a determination that the 8 alkonium clays listed below are safe under the intended conditions of use.

hydrogenated tallowalkonium bentonite*	benzalkonium montmorillonite*
quaternium-18/benzalkonium bentonite*	quaternium-90 montmorillonite
quaternium-90 bentonite	benzalkonium sepiolite*
stearalkonium bentonite	quaternium-90 sepiolite

\*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 data needed by the Panel are:

- Particle size distributions relevant for assessing potential inhalation exposures
- Percent alkonium cation in these ingredients that are releasable/exchangeable in formulation
- Repeated dose inhalation data at concentration of use (3.2%)
- Ocular irritation at concentration of use
- Confirmation that these ingredients are not used in powders

These ingredients are the products of the reactions of an ammonium salt with smectite clay and are reported to function as dispersing agents-nonsurfactant, emulsion stabilizers, and viscosity increasing agents-nonaqueous. Stearalkonium bentonite was reported to be used at a highest maximum concentration of 6.5% in nail polish and enamel.

### Alkyl Taurate Amides and Taurate Salts

The Panel issued a tentative report for public comment with the conclusion that 20 alkyl taurate amides and taurate salts are safe as used in cosmetics when formulated to be non-irritating. The highest reported maximum use concentration is up to 28% in bath products.

The ingredients reviewed in this report are:

potassium taurate*	sodium <i>n</i> -isostearoyl methyltaurate*
sodium methyltaurate	sodium lauroyl taurate
sodium taurate*	sodium methyl lauroyl taurate
calcium lauroyl taurate	sodium methyl myristoyl taurate
magnesium methyl cocoyl taurate*	sodium methyl oleoyl taurate
potassium cocoyl taurate*	sodium methyl palmitoyl taurate
potassium methyl cocoyl taurate	sodium methyl stearoyl taurate
sodium caproyl methyltaurate*	sodium methyltaurate isopalmitamide*
sodium cocoyl taurate	sodium methyltaurine cocoyl methyltaurate
sodium methyl cocoyl taurate	sodium taurine cocoyl methyltaurate*

\*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 amides and salts are large molecules and, therefore, are not expected to be inhaled. The Panel noted that the animal sensitization data were sufficient for determining the safety of these ingredients. Although there were no impurity data, the available, systemic toxicity studies raised no concerns and the negative genotoxicity assays were sufficient to address any concerns about carcinogenicity.

### Apple-derived Ingredients

*Pyrus malus* and *Malus domestica* are two genus and species names for apple. The Panel issues a tentative report for public comment with the conclusion that the following 25 apple-derived ingredients are safe in the present practices of use and concentration in cosmetics as described in this safety assessment, when formulated to be non-irritating and non-sensitizing.

Pyrus Malus (apple) bark extract*	Pyrus Malus (apple) pectin extract
Pyrus Malus (apple) carpel powder*	Pyrus Malus (apple) peel extract*
Pyrus Malus (apple) fiber*	Pyrus Malus (apple) peel powder
Pyrus Malus (apple) flower extract	Pyrus Malus (apple) peel wax*
Pyrus Malus (apple) fruit extract	Pyrus Malus (apple) pulp extract*
Pyrus Malus (apple) fruit	Pyrus Malus (apple) root bark powder*
Pyrus Malus (apple) fruit water	Pyrus Malus (apple) seed extract
Pyrus Malus (apple) juice	Pyrus Malus (apple) seed oil*
Pyrus Malus (apple) leaf extract*	

Malus Domestica (apple) callus extract  
Malus Domestica (apple) fiber  
Malus Domestica (apple) fruit extract  
Malus Domestica (apple) fruit water

Malus Domestica (apple) fruit cell culture extract  
Malus Domestica (apple) juice  
Malus Domestica (apple) oil  
Malus Domestica (apple) seed oil

The Panel concluded that the available data are insufficient for evaluating the safety of the following 3 apple-derived ingredients in cosmetic products:

Pyrus Malus (apple) root extract  
Pyrus Malus (apple) stem extract\*  
Malus Domestica (apple) stem extract

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

The data that are needed to evaluate the safety of these 3 ingredients are:

- Method of manufacture and impurities
- 28-day dermal toxicity study; if any adverse effects noted, genotoxicity and reproductive and developmental toxicity data may be needed

Because apple-derived ingredients may be obtained from different apple cultivars, the Panel noted that the composition of ingredients derived from different cultivars should be similar to the composition of ingredients reviewed in this safety assessment. The Panel discussed the study indicating that phloridzin, a component of apple root bark powder and apple leaf extract, has a stimulatory effect on melanogenesis, but agreed that a review of ingredients for drug effects (i.e., noncosmetic effects such as skin bleaching) is not within the Panel's purview. However, the Panel noted that an effect on cutaneous pigmentation would not be expected at the use concentrations of apple-derived ingredients in cosmetic products.

The Panel agreed that the safety test data on apple polyphenol extract and procyanidin B-2 in the report appendix should be incorporated into the body of the report. Apple polyphenol extract is actually a trade name for apple fruit extract, which is being reviewed in this safety assessment. Furthermore, apple polyphenol extract contains flavonoids, and procyanidin B-2 is a flavonoid that is present in apple fruit.

### **Inorganic Hydroxides**

The Panel issued a tentative report for public comment with the conclusion that the 4 inorganic hydroxides listed below are safe for use as pH adjusters or depilatories when formulated to be nonirritating, and are safe for use as hair straighteners under conditions of recommended use. Hairdressers should avoid skin contact and minimize consumer skin exposure.

calcium hydroxide  
magnesium hydroxide

potassium hydroxide  
sodium hydroxide

These inorganic hydroxides are reported to function as pH adjusters in cosmetic products. Study data demonstrate that the concentrations of inorganic hydroxides used in many cosmetic products can be irritating, even caustic, to the skin and eyes. However, the Panel recognized that while these ingredients may be dermal and/or ocular irritants, their uses as pH adjusters in cosmetic formulations dictates that most of the alkalinity will be neutralized to yield various salts. Furthermore, the concentration of the inorganic hydroxides used depends on the acid content of the formulations. Therefore, the concentration of free inorganic hydroxide is expected to be low in the formulations, and systemic toxicity is not expected to be a concern. The safety of inorganic hydroxides as pH adjusters should not be based on the concentration of use, but on the amount of free inorganic hydroxide that remains after neutralizing the formulation.

While not listed as a function in the *International Cosmetic Ingredient Dictionary and Handbook*, the Panel discussed the use of inorganic hydroxides as depilatories and hair straighteners at very high pH and concentration. If these hydroxides are used in hair care products, a limitation on use concentration and adequate instructions to hairdressers to avoid skin contact (such as by wearing gloves) and to minimize consumer skin exposure (by limiting the frequency of product use) would be adequate to assure that irritation is not a concern. The Panel noted that repeated applications of hair straighteners containing inorganic hydroxides by hairdressers to multiple clients over a period of time should be avoided unless adequate skin protection is provided.

Regarding the use of inorganic hydroxides in depilatories, the Panel recognizes that nearly all methods of hair removal cause some degree of irritation. Based on clinical experience of the Panel, although these chemicals have the potential to be severely irritating to the skin, clinically significant adverse reactions to these ingredients used in depilatories are not commonly seen. This suggests that current products are formulated to be practically nonirritating under conditions of recommended use. Formulators should take steps necessary to assure that current practices are followed. The conclusion notes that inorganic hydroxides in depilatories are safe when formulated to be non-irritating and safe as hair straighteners under conditions of recommended use (which include avoidance of contact with skin).

### **Monoglyceryl Monoesters**

The Panel issued a tentative amended report for public comment with the conclusion that the following 44 monoglyceryl monoesters are safe as used in cosmetics:

glyceryl acetate\*  
glyceryl adipate\*  
glyceryl arachidate\*  
glyceryl behenate  
glyceryl caprate  
glyceryl caprylate  
glyceryl caprylate/caprate

glyceryl citrate/lactate/linoleate/oleate  
glyceryl cocoate  
glyceryl cocoate/citrate/lactate\*  
glyceryl erucate\*  
glyceryl ethylhexanoate\*  
glyceryl ethylhexanoate/stearate/adipate  
glyceryl heptanoate\*

glyceryl hydrogenated rapeseedate\*  
 glyceryl hydrogenated rosinat  
 glyceryl hydrogenated soyate\*  
 glyceryl hydroxystearate  
 glyceryl isopalmitate\*  
 glyceryl isostearate  
 glyceryl isotridecanoate/stearate/ adipate  
 glyceryl lanolate  
 glyceryl laurate  
 glyceryl laurate SE\*  
 glyceryl laurate/oleate\*  
 glyceryl linoleate  
 glyceryl linolenate  
 glyceryl montanate\*  
 glyceryl oleate

glyceryl oleate SE\*  
 glyceryl oleate/elaidate  
 glyceryl olivate\*  
 glyceryl palmitate  
 glyceryl palmitate/stearate\*  
 glyceryl palmitoleate\*  
 glyceryl pentadecanoate\*  
 glyceryl ricinoleate  
 glyceryl ricinoleate SE  
 glyceryl rosinat  
 glyceryl stearate  
 glyceryl stearate SE  
 glyceryl stearate/malate  
 glyceryl tallowate\*  
 glyceryl undecylenate

\*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.

In 1982, the Panel concluded that glyceryl stearate and glyceryl stearate SE are safe for topical application to humans; this review includes the re-review of glyceryl stearate. Also included in this review are 34 previously reviewed ingredients, all of which were found safe as used in the original reviews (4). There are 8 additional cosmetic ingredients that have not yet been reviewed that are also included in this document. The monoglyceryl monoesters included in this report are similar to each other because they are structurally constituted of the esterification products of glycerin and carboxylic acids, the vast majority of which are fatty acids.

Several ingredients originally included in the 2004 safety assessment of glyceryl monoesters (i.e., glyceryl alginate, glyceryl arachidonate, glyceryl collagenate, glyceryl isostearate/myristate, glyceryl isostearates, glyceryl myristate, glyceryl polyacrylate, glyceryl sesquioleate, glyceryl sorbitol oleate/hydroxystearate, glyceryl stearate/acetate, glyceryl thiodipropionate, and glyceryl stearate/maleate) are not included in this re-review. In that report, the data were insufficient to support the safety of glyceryl arachidonate, and CIR does not routinely review ingredients that had insufficient data; that conclusion has since been reclassified as Use Not Supported. Glyceryl alginate, glyceryl isostearate/myristate, glyceryl myristate are included in other CIR safety assessments, and hence not included here. Glyceryl collagenate, glyceryl isostearates, glyceryl polyacrylate, glyceryl sesquioleate, glyceryl sorbitol oleate/hydroxystearate, glyceryl stearate/acetate and glyceryl thioglycolate are not appropriate for inclusion in this group and will be re-reviewed at another time. Lastly, glyceryl stearate/maleate is not a cosmetic ingredient, but was mistakenly included in the *International Cosmetic Ingredient Dictionary* at the time of the 2004 assessment, leading to its inclusion in that report.

With the exception of glyceryl rosinat and glyceryl hydrogenated rosinat (for which concentration of use has increased), the frequency of use of these ingredients has increased since the Panel's original review, but the concentration of use generally has not.

### Nonoxynols

The Panel issued a revised tentative amended report for public comment with the conclusion that the following 27 nonoxynols are safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating:

nonoxynol-1	nonoxynol-10	nonoxynol-25*
nonoxynol-2	nonoxynol-11*	nonoxynol-30
nonoxynol-3*	nonoxynol-12	nonoxynol-35*
nonoxynol-4	nonoxynol-13*	nonoxynol-40*
nonoxynol-5	nonoxynol-14	nonoxynol-44*
nonoxynol-6	nonoxynol-15	nonoxynol-50*
nonoxynol-7*	nonoxynol-18*	nonoxynol-70*
nonoxynol-8*	nonoxynol-20*	nonoxynol-100*
nonoxynol-9	nonoxynol-23	nonoxynol-120*

\*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 previously evaluated the safety of nonoxynols-2, -4, -8, -9, -10, -12, -14, -15, -30, -40, and -50 in cosmetics and issued a final report (published in 1983) with the conclusion that these nonoxynols are safe as cosmetic ingredients in the present practices of concentration and use. The Panel reevaluated the safety of nonoxynols-2, -4, and -8 and evaluated the safety of nonoxynols-1, -3, -5, -6, and -7 in cosmetics for the first time, and issued a final report (published in 1999) with the conclusion that nonoxynols-1, -2, -3, -4, -5, -6, -7, and -8 are safe as used in rinse-off products and safe at concentrations ≤ 5% in leave-on products. The 5% concentration limit was based on the potential for skin irritation. This conclusion modified a previous conclusion for nonoxynols-2, -4, and -8, which had been considered safe as used in both rinse-off and leave-on products.

At the September 2015 meeting, the Panel discussed the 5% concentration limit in response to correspondence received about a cosmetic product (cosmetic feminine wash – intended for use on the vaginal area) containing an unknown concentration of nonoxynol-9 that is being marketed within the United States, and based on knowledge of the irritation potential of spermicides containing nonoxynol-9. It was agreed that the concentration of nonoxynol-9 in this product should be obtained from the manufacturer. Additionally, the Panel removed the 5% concentration limit and issued a conclusion that, simply, cosmetic products containing nonoxynols should be formulated to be non-irritating.

Though the review of nonoxynol-9 as a spermicide (noncosmetic use) is not within the Panel's purview, data indicating that nonoxynol-9 spermicides cause mucous membrane irritation in animals and in humans are included in the Panel's safety evaluation of nonoxynols. Because all of the spermicides caused mucous membrane irritation, none of the studies demonstrated a safe level of exposure with respect to this endpoint. The Panel does not expect that spermicidal activity would be associated with use concentrations of nonoxynol-9 in cosmetic products, but would like to review the FDA over-the-counter drug (OTC) monograph on nonoxynol-9 or other data available from FDA for use concentrations in spermicide gels, indications of a concentration-response relationship for nonoxynol-9 and spermicidal activity, and adverse effects (e.g., mucous membrane irritation) associated with nonoxynol-9 use concentrations in spermicides. The Panel's revised tentative amended conclusion issued at this meeting will be reconsidered after these data have been reviewed.

## Silk Protein Ingredients

The Panel issued a tentative report for public comment with the conclusion that the following 8 silk protein ingredients are safe in the present practices of use and concentration in cosmetics as described in this safety assessment.

fibroin*	sericin
hydrolyzed fibroin	silk
hydrolyzed sericin	silk extract
hydrolyzed silk	silk powder

The Panel also concluded that the available data are insufficient for evaluating the safety of two silk protein ingredients, MEA-hydrolyzed silk\* and silkworm cocoon extract\*. The data that are needed to evaluate the safety of these two ingredients are:

- Method of manufacture and impurities
- Concentration of use
- 28-day dermal toxicity study; if absorbed, genotoxicity and reproductive and developmental toxicity data may be needed
- Skin irritation and sensitization data

\*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 reviewed a study in which an 8% sericin cream applied to the skin of renal patients caused depigmentation, but agreed that a review of ingredients for drug effects (i.e., noncosmetic effects) is not within the Panel's purview. However, the Panel noted that an effect on cutaneous pigmentation would not be expected at the use concentrations of silk protein ingredients in cosmetic products.

The Panel reviewed studies showing an association between asthma and dermal allergies to silk in children in China. They noted that the reported results of these studies are not sufficient to demonstrate that there is a cause-and-effect relationship between silk exposure and asthma, and that this issue is not relevant to the use of silk protein ingredients at use concentrations in cosmetic products. However, because some of the silk protein ingredients are used in products that may be inhaled, a statement relating to inhalation exposure and the absence of respiratory effects or systemic effects should be added to the report discussion. The Panel also agreed that the discussion should address the concern about pesticides and heavy metals, because of the available heavy metal impurities data on hydrolyzed silk and the indirect contamination of host plants during silkworm cultivation that may result from the use of pesticides.

## Insufficient Data Announcement

*For these insufficient data announcements, interested persons are given an opportunity to comment, provide information and/or request an oral hearing before the CIR Expert Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, and are available for review by any interested party. Please submit data and/or comments to CIR by **November 25, 2015, or sooner if possible**. These reports are scheduled for review by the CIR Expert Panel at its **December 14-15, 2015 meeting**.*

### Polymerized Tetramethylcyclotetrasiloxanes

The Panel issued an insufficient data announcement on the following 3 ingredients that are polymers of tetramethylcyclotetrasiloxane:

polysilicone-2  
polysilicone-4  
polysilicone-5

The Panel requested the following data for all three ingredients:

- Clarification that these polymers are only manufactured by covalently bonding them to colorant particles (in which case the INCI Dictionary does not accurately describe these ingredients) and that they do not exist, or are used, independently. Repeated dose inhalation
- Method of manufacture
- The amount that the polymers that are bonded to the surface of the particles; do the particles have a light or heavy load of the polymers (i.e., are the reactive sites of the particles partially or fully substituted with these siloxanes)
- Absorption/metabolism. If dermally absorbed: reproductive toxicity, 28-day dermal toxicity, and genotoxicity
- Impurity data for all three ingredients including residual allyl glycerol for polysilicone-5
- Physical and chemical properties, especially molecular weight ranges
- Information on whether percentages given in the concentration of use survey, are percentages of the polymers in the products or of the polymer/particle combination and how are these calculated

### Trimellitic Anhydride Copolymers

The Panel issued an insufficient data announcement for the following 6 ingredients:

adipic acid/CHDM/MA/neopentyl glycol/trimellitic anhydride copolymer  
adipic acid/neopentyl glycol/trimellitic anhydride copolymer

isostearoyl trimellitic anhydride/trimethylolpropane copolymer  
phthalic anhydride/trimellitic anhydride/glycols copolymer  
propylene glycol/sebacic acid/trimellitic anhydride copolymer  
trimethylpentanediol/isophthalic acid/trimellitic anhydride copolymer

The data that are needed to evaluate the safety of these 6 ingredients are:

- Molecular weight;
- Method of manufacture and impurities data, specifically, the amount of residual monomer in each copolymer;
- Metabolism data, specifically, are these ingredients metabolized in the skin;
- Dermal absorption; if absorbed, then genotoxicity and reproductive toxicity data are needed;
- Irritation and sensitization data at the maximum leave-on concentration of 1% adipic acid/neopentyl glycol/trimellitic anhydride copolymer; however, if there are leave-on uses at higher concentrations, and/or with other ingredients, test data should be submitted at those concentrations and/or for those ingredients, as well; and
- Irritation and sensitization data relating to nail use.

Additionally, some of the reported uses are in “other manicuring preparations”. The Panel would like clarification of the other uses.

### Hexamethylene Diisocyanate (HDI) Polymers

The Panel reviewed the safety of hexamethylene diisocyanate (HDI) polymers and issued an Insufficient Data Announcement for the following 19 ingredients:

HDI/trimethylol hexyllactone crosspolymer  
bis-C16-20 isoalkoxy TMHDI/PEG-90 copolymer  
bis-hydroxyethyl acrylate poly(1,4-butanediol)-9/TMHDI copolymer\*  
bis-isostearyl 1,4-butanediol/HDI/hydrogenated dimer dilinoleyl alcohol copolymer\*  
bis-lauryl cocaminopropylamine/HDI/PEG-100 copolymer\*  
bis-methoxy PEG-10 dimethyl MEA/HDI/bis-PEG-10 dimethicone copolymer\*  
1,4-butanediol/succinic acid/adipic acid/HDI copolymer\*  
cholesterol/HDI/pullulan copolymer\*  
decyl HDI/PEG-180 crosspolymer\*  
diethylene glycol/DMAP acrylamide/ PEG-180/HDI copolymer  
HDI/Di-C12-14 alkyl tartrate/hydrogenated dilinoleyl alcohol copolymer  
HDI/PEI-45/SMDI crosspolymer\*  
HDI/PPG/polycaprolactone crosspolymer  
methoxy PEG-17/methoxy PEG-11/HDI crosspolymer  
methoxy PEG-17/methoxy PEG-11/HDI isocyanurate trimer crosspolymer\*  
PEG-240/HDI copolymer bis-decyltetradeceth-20 ether  
PPG-26/HDI copolymer\*  
steareth-100/PEG-136/HDI copolymer  
stearyl HDI/PEG-50 copolymer\*

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

- Method of manufacturing with regards to end capping, and quantification of any residual end-capping agents
- Stability of these ingredients in formulation
- Quantification of any residual diisocyanate, including HDI, trimethylhexanediisocyanate (TMHDI), and saturated decyl methylene diphenyldiisocyanate (SMDI)
- HRIPT of HDI/trimethylol hexyllactone crosspolymer at the greatest concentration of use (31%) or higher
- Repeated dose inhalation data

Exposure to diisocyanates (such as HDI) in the work place is one of the leading causes of occupational asthma, and has been associated with airway irritation and asthma-like symptoms, hypersensitivity pneumonitis, rhinitis, and accelerated lung deterioration. Diisocyanates can also cause both irritant and allergic contact dermatitis, as well as skin and conjunctival irritation. Thus, the data requested are needed to be sure that these diisocyanate monomers are neither present in the ingredients as manufactured, nor are released in formulations.

## Re-Reviews

### Chamomile recutita-Derived Ingredients – reopened

At the December 2013 CIR Expert Panel meeting, a final report on Chamomilla recutita-derived ingredients was issued with the conclusion that the flower-derived ingredients were safe when formulated to be non-sensitizing, while the data were insufficient for the ingredients derived from other parts of the plant. The CIR Expert Panel requested chemical composition data on ingredients derived from the whole plant and the leaves and stem.

Industry provided additional information to support the safety of ingredients derived from other plant parts. Based on the additional information, the Panel voted to reopen the report. The Panel is still concerned about the lack of information on the composition of the roots. Therefore, while ingredients containing leaves and stems may be moved to the safe when formulated to be non-sensitizing conclusion, the whole plant extract, Chamomilla Recutita (Matricaria) Extract may remain with an insufficient data conclusion.

## **Methylisothiazolinone – not reopened**

The Panel reviewed the June 2015 SCCS opinion on Methylisothiazolinone (MI) and noted that they looked at the same information as the SCCS but came out with a different conclusion. In September 2014, “the CIR Expert Panel concluded that MI is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when they are formulated to be non-sensitizing, which may be determined based on a QRA.” Although the Panel voted not to open the report on MI, they indicated that they will be monitoring reports of sensitization rates to this preservative.

## **136<sup>th</sup> Meeting Notes**

### **Director’s Report**

Dr. Gill reported on the expanding involvement of CIR in the global community. Earlier this month, the China Association of Fragrances, Flavor and Cosmetic Industries (CAFFCI) invited CIR to participate in their International Forum on the Safety Evaluation of Cosmetic Ingredients. Attendees included authorities from China FDA and the provinces, academics from various universities in China and a representative from the US FDA’s China Office. The focus was CIR – the role of CIR in US risk management practices, CIR processes and procedures, and the use of CIR conclusions in industry. Dr. Bergfeld and Dr. Heldreth represented CIR. Members from the Council and a representative from the CIR SSC also participated. CIR received very positive feedback from attendees on the presentation as well as the CIR approach to assessing cosmetic safety. They would like to establish an on-going collaboration with CIR.

CIR assistant director and senior writer Monice Fiume was the featured speaker for a webinar for industry and officials in Canada. She fielded numerous questions about the CIR process and her talk was also well received. In early November, Dr. Boyer will present CIR to the Korean government and industry representatives, and CIR has been approached about sharing the CIR model with officials in South America next year.

CIR staff presented for Panel discussion their internal review of the format used to develop safety assessments. This work is part of CIR’s on-going efforts to improve, where needed, the consistency in format and data quality standards of CIR safety assessments. There were substantive changes proposed to the guidance in the toxicological studies sections. The Panel discussed the alternatives provided and proposed changes will be consolidated and discussed at the next meeting.

Dr. Gill mentioned that Dr. Robert Califf has been nominated for Commissioner of FDA. Since February, he has served as the Deputy Commissioner for medical products and tobacco. Dr. Califf is a cardiologist in academic medicine at Duke University and the co-founder of the Duke Clinical Research Institute. He is awaiting Senate confirmation.

Finally, Dr. Gill welcomed a new scientific analyst/writer to the CIR staff. Laura Scott joined the CIR team in August. She has a background as a research scientist with experience in developing bioanalytical methods and preparing technical reports for the pharmaceutical industry. Ms. Scott received her BS in Biochemistry and her MS in Analytical Chemistry from Virginia Polytechnic Institute.

### **Report Strategies**

The Panel was asked to provide input on the review strategies for the remaining Citrus-derived ingredients (peel essential oils and fruit-derived ingredients already reviewed) and the remaining hydrolyzed protein ingredients. The CIR Expert Panel recommended that the citrus ingredients continue to be reviewed by plant part and suggested peel-derived preparations be reviewed next, followed by the flower and leaf preparations and then the remaining ingredients. The CIR Expert Panel recommended that they continue to review hydrolyzed proteins by source based on uses reported to the VCRP. They did note that ingredients derived from skin proteins, such as collagen, actin and elastin could be reviewed in one report.”

### **Reports Tabled**

#### **Citrus Fruit – Derived Ingredients**

The Panel tabled the draft final report on the 80 *Citrus* fruit-derived ingredients listed below in order to allow time for the CIR staff to clarify the inclusion of data from the International Fragrance Association (IFRA) regarding 7-methoxycoumarin in the discussion of the report. Staff will also draft language for the discussion regarding the findings of an epidemiological study on melanoma and the possible link to citrus consumption. The Panel found there were no concerns due to the lack of some controls and hazard ratios including background levels.

citrus aurantifolia (lime)/citrus limon (lemon) fruit water\*  
citrus aurantifolia (lime) fruit\*  
citrus aurantifolia (lime) fruit extract  
citrus aurantifolia (lime) fruit water\*  
citrus aurantifolia (lime) juice  
citrus aurantium amara (bitter orange) fruit extract  
citrus aurantium amara (bitter orange) fruit juice extract\*  
citrus aurantium bergamia (bergamot) fruit extract  
citrus aurantium bergamia (bergamot) fruit water\*  
citrus aurantium dulcis (orange) fruit extract  
citrus aurantium dulcis (orange) fruit powder\*  
citrus aurantium dulcis (orange) fruit water

citrus aurantium dulcis (orange) juice  
citrus aurantium sinensis (orange) fiber  
citrus clementina fruit extract\*  
citrus clementina juice\*  
citrus depressa fruit extract\*  
citrus depressa fruit water\*  
citrus glauca fruit extract  
citrus grandis (grapefruit) fruit extract  
citrus grandis (grapefruit) fruit/peel water  
citrus grandis (grapefruit) fruit water  
citrus grandis (grapefruit) juice  
citrus grandis/paradisi fruit water\*

citrus hassaku fruit extract\*  
citrus hassaku/natsudaidai fruit juice\*  
citrus hassaku/natsudaidai fruit powder\*  
citrus iyo fruit extract\*  
citrus iyo fruit water\*  
citrus jabara juice\*  
citrus japonica fruit extract  
citrus junos fruit extract  
citrus junos fruit juice\*  
citrus junos fruit oil\*  
citrus junos fruit powder\*  
citrus junos fruit water\*  
citrus limon (lemon) fruit extract  
citrus limon (lemon) fruit oil\*  
citrus limon (lemon) fruit powder\*  
citrus limon (lemon) fruit water

citrus limon (lemon) juice  
citrus limon (lemon) juice extract  
citrus limon (lemon) juice powder\*  
citrus madurensis fruit extract  
citrus madurensis fruit juice\*  
citrus medica vulgaris fruit extract  
citrus nobilis (mandarin orange) fruit extract  
citrus nobilis (mandarin orange) fruit juice  
citrus paradisi (grapefruit) fruit extract  
citrus paradisi (grapefruit) fruit water\*  
citrus paradisi (grapefruit) juice\*  
citrus reticulata (tangerine) fruit\*  
citrus reticulata (tangerine) fruit extract  
citrus reticulata (tangerine) fruit water\*  
citrus shunkokan fruit extract\*  
citrus sinensis (orange) fruit extract  
citrus sinensis (orange) fruit water  
citrus sphaerocarpa fruit juice\*  
citrus sudachi fruit extract\*  
citrus sudachi fruit juice\*  
citrus tachibana/reticulata fruit juice\*  
citrus tamurana fruit extract\*  
citrus tangelo fruit juice\*  
citrus tangelo fruit powder\*  
citrus tangerina (tangerine) fruit\*  
citrus tangerina (tangerine) fruit water\*  
citrus tankan fruit extract\*  
citrus tankan fruit water\*  
citrus unshiu/citrus reticulata/citrus iyo fruit water\*  
citrus unshiu fruit extract\*  
citrus unshiu fruit juice\*  
citrus unshiu fruit juice ferment extract filtrate  
citrus unshiu fruit oil\*  
citrus unshiu fruit powder\*  
citrus unshiu fruit water\*  
citrus unshiu/sinensis/reticulata fruit extract\*  
defatted citrus unshiu fruit\*  
hydrolyzed citrus aurantium dulcis fruit extract  
microcitrus australasica fruit extract\*  
microcitrus australis fruit extract

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

## Scientific Literature Reviews

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

1-Hydroxyethyl-4,5-Diaminopyrazole Sulfate  
Helianthus Annuus (Sunflower)-derived ingredients

Draft reports for these ingredient families, along with any unpublished data submitted by interested parties, may be presented to the Panel at its meeting on December 14-15, 2015.

- These literature reviews are currently under development and some may be reviewed at the next meeting.

algae ingredients  
acryloyldimethyltaurate polymers  
alkoxyl alkyl silanes phosphoric acid, its simple salts, & the metaphosphates  
*Ginkgo biloba*-derived ingredients  
keratin proteins  
polyglyceryl fatty acid esters  
Shea-derived ingredients  
simple carbonate salts  
*Rosa canina*-derived ingredients

- Re-reviews scheduled for the next Panel meeting

sodium sulfate

**Next CIR Expert Panel Meeting**

Monday and Tuesday, December 14-15, 2015, at The Hilton – DoubleTree Hotel, Washington, DC 20005 --- Please contact Carla Jackson ([jacksonc@cir-safety.org](mailto:jacksonc@cir-safety.org)) at CIR before the meeting if you plan to attend.