Announcement

Cosmetic Ingredient Review Expert Panel
125th Meeting (December 10-11, 2012) - Findings

December 14, 2012

● **Final Safety Assessments**
- **PEGylated oils – 130 ingredients**
- **Tin(IV) Oxide – 1 ingredient**

● **Tentative and Tentative Amended Safety Assessments**
- **Alkyl esters – 239 ingredients**
- **Alkyl ethylhexanoates – 16 ingredients**
- **6-Hydroxyindole – 1 ingredient**
- **Hypericum perforatum-derived ingredients – 7 ingredients**
- **Methyl glucose polyethers & esters – 25 ingredients**
- **Modified terephthalate polymers – 6 ingredients**
- **Nylon polymers - 8 ingredients**
- **Talc – 1 ingredient**

● **Insufficient Data Announcement**
- **Plant- and animal-derived amino acids and hydrolyzed proteins – 75 ingredients**

● **Re-review and New Data**
- **2-Amino-6-chloro-4-nitrophenol – not reopened**
- **m-Phenylenediamine and m-phenylenediamine sulfate – not reopened**
- **PEGs cocamine- reopened to amend conclusion and add ingredients – 47 ingredients**
- **Phthalates – not reopened**

● **125th Meeting Notes**
- **Director's report**
- **Hair dye self-testing presentation – Dr. Carsten Goebel**
- **Infant skin presentation – Dr. Ivan Boyer**
- **Report tabled - Achillea millefolium-derived ingredients**
- **Scientific literature reviews posted on the CIR website**
  - **for ingredients that may be considered at the next Panel meeting**
    - boron nitride
    - nitrocellulose
    - palmitoyl oligopeptide
    - tromethamine
- **Re-reviews for the next Panel meeting**
- **Scientific Literature Reviews under development**
- **Next CIR Expert Panel Meeting – Monday and Tuesday, March 18-19, 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 Unpublished data cited as references in CIR safety assessments are posted on the CIR website and available for review at the CIR office. Final safety assessments and final amended safety assessments will be posted on the CIR website at www.cir-safety.org.

PEGylated Oils

The CIR Expert Panel issued a final amended safety assessment with the conclusion that PEGylated oils are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating. This conclusion supersedes the earlier conclusion issued by the Expert Panel in 1997 for PEGs castor oils. The 130 ingredients included in this safety assessment are:

PEG-2 castor oil*
PEG-3 castor oil*
PEG-4 castor oil*
PEG-5 castor oil*
PEG-8 castor oil*
PEG-9 castor oil
PEG-10 castor oil*
PEG-11 castor oil*
PEG-15 castor oil*
PEG-16 castor oil*
PEG-20 castor oil*
PEG-25 castor oil
PEG-26 castor oil*
PEG-29 castor oil*
PEG-30 castor oil
PEG-33 castor oil
PEG-35 castor oil
PEG-36 castor oil
PEG-40 castor oil
PEG-44 castor oil*
PEG-50 castor oil
PEG-54 castor oil*
PEG-55 castor oil*
PEG-60 castor oil
PEG-75 castor oil*
PEG-80 castor oil*
PEG-100 castor oil*
PEG-200 castor oil*
PEG-18 castor oil dioleate*
PEG-60 castor oil isostearate*
PEG-2 hydrogenated castor oil
PEG-5 hydrogenated castor oil*
PEG-6 hydrogenated castor oil*
PEG-7 hydrogenated castor oil
PEG-8 hydrogenated castor oil*
hydrogenated castor oil PEG-8 esters*
PEG-10 hydrogenated castor oil
PEG-16 hydrogenated castor oil
PEG-20 hydrogenated castor oil
PEG-25 hydrogenated castor oil
PEG-30 hydrogenated castor oil
PEG-35 hydrogenated castor oil
PEG-40 hydrogenated castor oil
PEG-45 hydrogenated castor oil
PEG-50 hydrogenated castor oil
PEG-54 hydrogenated castor oil*
PEG-55 hydrogenated castor oil*
PEG-60 hydrogenated castor oil
PEG-65 hydrogenated castor oil*
PEG-80 hydrogenated castor oil
PEG-100 hydrogenated castor oil
PEG-200 hydrogenated castor oil*
PEG-5 hydrogenated castor oil isostearate*
PEG-10 hydrogenated castor oil isostearate*
PEG-15 hydrogenated castor oil isostearate*
PEG-20 hydrogenated castor oil isostearate*
PEG-30 hydrogenated castor oil isostearate*
PEG-40 hydrogenated castor oil isostearate*
PEG-50 hydrogenated castor oil isostearate*
PEG-58 hydrogenated castor oil isostearate*
PEG-20 hydrogenated castor oil laurate*
PEG-30 hydrogenated castor oil laurate*
PEG-40 hydrogenated castor oil laurate*
PEG-50 hydrogenated castor oil laurate*
PEG-60 hydrogenated castor oil laurate*
PEG-20 hydrogenated castor oil pca isostearate*
PEG-30 hydrogenated castor oil pca isostearate*
PEG-40 hydrogenated castor oil pca isostearate
PEG-60 hydrogenated castor oil pca isostearate*
PEG-50 hydrogenated castor oil succinate
potassium PEG-50 hydrogenated castor oil succinate*
sodium PEG-50 hydrogenated castor oil succinate*
PEG-5 hydrogenated castor oil triisostearate*
PEG-10 hydrogenated castor oil triisostearate*
PEG-15 hydrogenated castor oil triisostearate*
PEG-20 hydrogenated castor oil triisostearate
PEG-30 hydrogenated castor oil triisostearate*
PEG-40 hydrogenated castor oil triisostearate
PEG-50 hydrogenated castor oil triisostearate*
PEG-60 hydrogenated castor oil triisostearate*
adansonia digitata seed oil PEG-8 esters*
almond oil PEG-6 esters*
almond oil PEG-8 esters *
apricot kernel oil PEG-6 esters
apricot kernel oil PEG-8 esters*
apricot kernel oil PEG-40 esters*
argan oil PEG-8 esters*
avocado oil PEG-8 esters*
avocado oil PEG-11 esters
bertholletia excelsa seed oil PEG-8 esters*
borage seed oil PEG-8 esters*
coconut oil PEG-10 esters
corn oil PEG-6 esters*
corn oil PEG-8 esters*
grape seed oil PEG-8 esters
hazel seed oil PEG-8 esters*
hydrogenated palm/palm kernel oil PEG-6 esters
jojoba oil PEG-8 esters
jojoba oil PEG-150 esters*
linseed oil PEG-8 esters*
macadamia ternifolia seed oil PEG-8 esters*
mango seed oil PEG-70 esters*
mink oil PEG-13 esters*
olive oil PEG-6 esters*
olive oil PEG-7 esters
olive oil PEG-8 esters*
olive oil PEG-10 esters
orbignya oleifera seed oil PEG-8 esters*
palm oil PEG-8 esters*
passiflora edulis seed oils PEG-8 esters*
peanut oil PEG-6 esters*
PEG-75 crambe abyssinica seed oil*
PEG-75 meadowfoam oil
pumpkin seed oil PEG-8 esters*
rapeseed oil PEG-3 esters*
rapeseed oil PEG-20 esters*
raspberry seed oil PEG-8 esters*
safflower seed oil PEG-8 esters*
schinziophyton rautanenii kernel oil PEG-8 esters*
sclerocarya birrea seed oil PEG-8 esters*
sesame seed oil PEG-8 esters*
soybean oil PEG-8 esters*
soybean oil PEG-20 esters*
soybean oil PEG-36 esters*
sunflower seed oil PEG-8 esters*
sunflower seed oil PEG-32 esters*

sweet almond oil PEG-8 esters*
watermelon seed oil PEG-8 esters*
wheat germ oil PEG-40 butyloctanol esters*
wheat germ oil PEG-8 esters*

*Not reported to be in current use. Were ingredients in this group 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.

PEGylated Oils is the name CIR devised to describe this large group of cosmetic ingredients. These ingredients are mixtures of the etherification and transesterification products of fatty acid glycerides and fatty acids from plant sources and equivalents of ethylene oxide to produce the desired PEG length. Because of the nature of the process by which these ingredients are produced, PEG compounds unattached to glycerides or fatty acid groups will be present,. Overall, PEGylated oils are complex mixtures of structurally related molecules. The Panel determined that the available data in previous safety assessments of PEGs and of plant-derived fatty acids strongly supported the safety of PEGylated oils. In addition, the Panel considered that the available data on PEGs castor oils and PEGs hydrogenated castor oils could be "read across" to support the safety of the entire group.

The Expert Panel recognized that these ingredients can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption, or when dermal absorption was a concern.

The Expert Panel noted that the earlier safety assessment of PEG castor oils specified safe up to a 50% use concentration. As PEGs castor oils and the rest of the PEGylated oils now are used at concentrations below 50% in leave-on products, the Panel determined that a concentration limit need no longer be specified. Products using these ingredients should be formulated to be non-irritating.

Tin(IV) Oxide

The CIR Expert Panel issued a final safety assessment with the conclusion that tin(IV) oxide is safe in the present practices of use and concentration in cosmetics.

This ingredient is a widely used cosmetic abrasive, bulking, and opacifying agent. Throughout the report, the valence of tin oxide used in studies was specified and, if not available, the absence of this information was noted. The Panel asserted that, while there were no carcinogenicity or reproductive and developmental toxicity data, these endpoints were not of concern because this ingredient is insoluble and would not be absorbed through the skin.

Tentative Safety Assessments

These tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before December 21, 2012. 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, posted on the CIR website, and are available at the CIR office for review by any interested party. ***Please submit data and/or comments to CIR by February 18, 2013, or sooner if possible.*** *These reports may be scheduled for review by the CIR Expert Panel at its* ***March 18-19, 2013 meeting.***

Alkyl Esters

The CIR Expert Panel issued a tentative amended safety assessment for public comment with the conclusion that the 239 alkyl esters listed below are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

arachidyl behenate arachidyl erucate*
arachidyl propionate
batyl isostearate*
batyl stearate*
behenyl beeswax
behenyl behenate
behenyl erucate
behenyl isostearate*
behenyl olivate
behenyl/isostearyl beeswax*
butyl avocadate
butyl babassuate*
butyl isostearate*
butyl myristate
butyl oleate*
butyl stearate
butyloctyl beeswax*
butyloctyl behenate*
butyloctyl candelillate*
butyloctyl cetearate*
butyloctyl oleate*
butyloctyl palmitate*
C10-40 isoalkyl acid octyldodecanol esters*
C14-30 alkyl beeswax*
C16-36 alkyl stearate*
C18-38 alkyl beeswax*
C18-38 alkyl c24-54 acid ester*
C20-40 alkyl behenate*
C20-40 alkyl stearate
C30-50 alkyl beeswax*
C30-50 alkyl stearate*
c32-36 isoalkyl stearate*
C40-60 alkyl stearate*
C4-5 isoalkyl cocoate*
caprylyl butyrate*
caprylyl caprylate
caprylyl eicosenoate
cetearyl behenate
cetearyl candelillate
cetearyl isononanoate
cetearyl nonanoate*
cetearyl olivate
cetearyl palmate*
cetearyl palmitate*
cetearyl rice branate*
cetearyl stearate
cetyl babassuate
cetyl behenate*
cetyl caprate
cetyl caprylate
cetyl dimethyloctanoate*
cetyl esters
cetyl isononanoate*
cetyl laurate
cetyl myristate
cetyl myristoleate*
cetyl oleate*
cetyl palmitate
cetyl ricinoleate
cetyl stearate
cetyl tallowate
chimyl isostearate*
chimyl stearate*
coco-caprylate
coco-caprylate/caprate
coco-rapeseedate*
decyl castorate*
decyl cocoate
decyl isostearate*
decyl jojobate*
decyl laurate*
decyl myristate*
decyl oleate
decyl olivate
decyl palmitate*
decyltetradecyl cetearate*
erucyl arachidate*
erucyl erucate*
erucyl oleate*
ethylhexyl adipate/palmitate/stearate*
ethylhexyl C10-40 isoalkyl acidate*
ethylhexyl cocoate
ethylhexyl hydroxystearate
ethylhexyl isononanoate
ethylhexyl isopalmitate
ethylhexyl isostearate
ethylhexyl laurate
ethylhexyl myristate
ethylhexyl neopentanoate*
ethylhexyl oleate*
ethylhexyl olivate
ethylhexyl palmitate
ethylhexyl pelargonate
ethylhexyl stearate
heptyl undecylenate
heptylundecyl hydroxystearate

hexyl isostearate
hexyl laurate
hexyldecyl hexyldecanoate*
hexyldecyl isostearate
hexyldecyl laurate
hexyldecyl oleate*
hexyldecyl palmitate*
hexyldecyl stearate
hexyldodecyl/octyldecyl hydroxystearate*
hydrogenated castor oil behenyl esters*
hydrogenated castor oil cetyl esters *
hydrogenated castor oil stearyl esters*
hydrogenated ethylhexyl olivate
hydrogenated ethylhexyl sesamate*
hydrogenated isocetyl olivate*
hydrogenated isopropyl jojobate*
hydroxycetyl isostearate*
hydroxyoctacosanyl hydroxystearate
isoamyl laurate
isobutyl myristate*
isobutyl palmitate*
isobutyl perlargonate*
isobutyl stearate*
isobutyl tallowate*
isocetyl behenate*
isocetyl isodecanoate*
isocetyl isostearate*
isocetyl laurate*
isocetyl myristate
isocetyl palmitate
isocetyl stearate
isodecyl cocoate
isodecyl hydroxystearate*
isodecyl isononanoate
isodecyl laurate
isodecyl myristate
isodecyl neopentanoate
isodecyl oleate
isodecyl palmitate*
isodecyl stearate*
isohexyl caprate
isohexyl laurate*
isohexyl neopentanoate*
isohexyl palmitate*
isolauryl behenate*
isononyl isononanoate
isooctyl caprylate/caprate*
isooctyl tallate*
isopropyl isostearate
isopropyl arachidate*
isopropyl avocadate*
isopropyl babassuate*
isopropyl behenate*
isopropyl hydroxystearate
isopropyl isostearate
isopropyl jojobate
isopropyl laurate*
isopropyl linoleate
isopropyl myristate
isopropyl oleate*
isopropyl palmitate
isopropyl ricinoleate
isopropyl sorbate*
isopropyl stearate
isopropyl tallowate*
isostearyl avocadate
isostearyl behenate
isostearyl erucate*
isostearyl hydroxystearate
isostearyl isononanoate
isostearyl isostearate
isostearyl laurate
isostearyl linoleate
isostearyl myristate
isostearyl neopentanoate
isostearyl palmitate
isotridecyl isononanoate
isotridecyl laurate*
isotridecyl myristate*
isotridecyl stearate
lauryl behenate*
lauryl cocoate*
lauryl isostearate*
lauryl laurate
lauryl myristate*
lauryl oleate/
lauryl palmitate
lauryl stearate/
lignoceryl erucate*
myristyl isostearate*
myristyl laurate
myristyl myristate
myristyl neopentanoate
myristyl stearate
octyldecyl oleate*
octyldodecyl avocadoate*
octyldodecyl beeswax*
octyldodecyl behenate*
octyldodecyl cocoate*
octyldodecyl erucate
octyldodecyl hydroxystearate*
octyldodecyl isostearate
octyldodecyl meadowfoamate*
octyldodecyl myristate
octyldodecyl neodecanoate*
octyldodecyl neopentanoate
octyldodecyl octyldodecanoate
octyldodecyl oleate*
octyldodecyl olivate
octyldodecyl ricinoleate
octyldodecyl safflowerate*
octyldodecyl stearate
oleyl arachidate*
oleyl erucate
oleyl linoleate
oleyl myristate*
oleyl oleate
oleyl stearate*
propylheptyl caprylate
stearyl beeswax
stearyl behenate*
stearyl caprylate
stearyl erucate*
stearyl heptanoate
stearyl linoleate*
stearyl olivate
stearyl palmitate
stearyl stearate
tetradecyleicosyl stearate*
tetradecyloctadecyl behenate*
tetradecyloctadecyl hexyldecanoate*
tetradecyloctadecyl myristate*
tetradecyloctadecyl stearate
tetradecylpropionates*
tridecyl behenate*
tridecyl cocoate*
tridecyl erucate*
tridecyl isononanoate
tridecyl laurate*
tridecyl myristate*
tridecyl neopentanoate
tridecyl stearate

*Not 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 core relationship between these ingredients is a carboxyl ester functional group flanked on both sides by alkyl chains. These ingredients are reported to function in cosmetics mostly as skin conditioning agents. Although there are data gaps in this report, the relatedness of molecular structures, physicochemical properties, and functions and concentrations in cosmetics allow grouping these ingredients together and interpolating the available toxicological data to support the safety of the entire group. The available data on many of the ingredients, especially the previously reviewed ingredients, and on some of the constituent alcohols and acids, are sufficient, and similar structure-property relationships, biologic characteristics, and cosmetic product usage suggest that the available data may be extrapolated to support the safety of the entire group. For example, a concern was expressed regarding the extent of dermal absorption for certain long-chain, branched alkyl esters because of a lack of information on dermal absorption and metabolism. The consensus of the Panel was that because dermal penetration of long-chain alcohols is likely to be low, and the dermal penetration for alkyl esters is likely to be even lower, inferring safety from ingredients where toxicity data were available was appropriate. Data on previously reviewed ingredients and on some of the constituent alcohols and acids also proved useful in determining the safety of the entire group.

Alkyl Ethylhexanoates

The CIR Expert Panel issued a tentative amended safety assessment for public comment with the conclusion that the 16 alkyl ethylhexanoates listed below are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

C12-13 alkyl ethylhexanoate
C12-15 alkyl ethylhexanoate
C14-18 alkyl ethylhexanoate*
cetearyl ethylhexanoate
cetyl ethylhexanoate
decyltetradecyl ethylhexanoate*
ethylhexyl ethylhexanoate
hexyldecyl ethylhexanoate*
isocetyl ethylhexanoate
isodecyl ethylhexanoate*
isostearyl ethylhexanoate*
lauryl ethylhexanoate*
myristyl ethylhexanoate*
octyldodecyl ethylhexanoate*
stearyl ethylhexanoate
tridecyl ethylhexanoate

*Not 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 ingredients in this report are branched alkyl esters that are the result of the esterification of an alkyl alcohol with 2-ethylhexanoic acid or its chloride salt. The core relationship is the same as for the alkyl esters group described above, namely, a carboxyl ester functional group flanked on both sides by alkyl chains. This group was separated from the alkyl esters safety assessment to focus attention on the potential liver and developmental toxicity of 2-ethylhexanoic acid, a possible metabolite of the alkyl ethylhexanoates. It has been postulated that, in animal studies of 2-ethylhexanoic acid, maternal liver toxicity could begin a cascade of effects that includes metallothionein (MT) induction, zinc accumulation in the liver due to MT binding, and a resulting zinc deficiency in the developing embryo. The Panel determined that results of animal tests with di-2-ethylhexyl terephthalate (a 2-ethylhexanoic acid precursor used as a model for exposure without liver toxicity) suggested that the process of metabolic conversion results in a time course that allows clearance of 2-ethylhexanoic acid before sufficient levels can arise to produce toxicity.

The rationale described above applied to the entire group of alkyl ethylhexanoates. Additionally, the similar chemical structures, physicochemical properties, functions, and concentrations in cosmetics allow interpolation of the available toxicological data to support the safety of the entire group.

6-Hydroxyindole

The CIR Expert Panel issued a tentative safety assessment for public comment with a conclusion that 6-hydroxyindole is safe as a hair dye ingredient in the present practices of use and concentration.

The CIR Expert Panel expressed concern that 6-hydroxyindole appears to be a photosensitizer at a concentration of 5%; however, further data did not indicate photosensitization at 2%. The Panel noted that this ingredient has 105 uses in hair dye products at concentrations up to 0.5%. The Expert Panel recognized that 6-hydroxyindole functions as a hair dye ingredient and that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act, when the product label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel considered the concerns about such self-testing (see discussion under 125th Meeting Notes), but agreed that there was not a sufficient basis for changing this advice to consumers at this time. The Expert Panel continues to expect that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures, but awaits data currently under development by the industry to shed further light on this practice.

Hypericum perforatum-derived ingredients

The CIR Expert Panel issued a tentative amended safety assessment for public comment for the 7 hypericum perforatum-derived ingredients listed below with the conclusion that they are safe in the present practices of use and concentration as described in the safety assessment.

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

One common name for *Hypericum perforatum* is St. John's wort. These ingredients function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; skin protectants; antioxidants, hair conditioning agents; and antimicrobial agents. Data were submitted to address the insufficient data conclusion of the original report on hypericum perforatum extract and hypericum perforatum oil. The Panel was satisfied that the data address the concentration of use, function, photosensitization/phototoxicity, reproductive/developmental toxicity, irritation/sensitization, and ocular irritation data needs from that original safety assessment. The Panel also added the following 5 other ingredients derived from *H. perforatum* to the group: hypericum perforatum flower extract;hypericum perforatum flower/leaf extract; hypericum perforatum flower/leaf/stem extract; hypericum perforatum flower/twig extract; and hypericum perforatum leaf extract.

The Panel also noted that the discussion section of the safety assessment report for of these ingredients would appropriately includewill mention of the presence of photoactive constituents of plant extracts, such as hypericin and quercetin, but that the concentrations of such constituents are not at a high level in the Hypericum perforatum-derived ingredients, and that the ingredients themselves are used at low concentrations.

The Panel decided not to add hypericum callus culture extract because it is produced differently (plant cells grown in culture), compared with the other extracts considered, and its composition was uncertain.

Methyl Glucose Polyethers and Esters

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

Ethers:	*polyethers*	*Esters and polyethers:*
methyl glucose caprylate/caprate*	PPG-10 methyl glucose ether	PEG-120 methyl glucose dioleate
methyl glucose dioleate	PPG-20 methyl glucose ether	PEG-20 methyl glucose distearate
methyl glucose isostearate*	PPG-25 methyl glucose ether*	PEG-80 methyl glucose laurate*
methyl glucose laurate*	PPG-20 methyl glucose ether acetate*	PEG-20 methyl glucose sesquicaprylate/ sesquicaprate*
methyl glucose sesquicaprylate/ sesquicaprate*	PPG-20 methyl glucose ether distearate	PEG-20 methyl glucose sesquilaurate*
methyl glucose sesquicocoate*	methyl gluceth-10	PEG-20 methyl glucose sesquistearate
methyl glucose sesquiisostearate	methyl gluceth-20	PEG-120 methyl glucose triisostearate*
methyl glucose sesquilaurate*		PEG-120 methyl glucose trioleate
methyl glucose sesquioleate		
methyl glucose sesquistearate		

*not 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 reportedly function as skin and hair conditioning agents, whereas, the methyl glucose esters function only as skin conditioning agents in cosmetic products.

The Panel noted the absence of dermal penetration, reproductive and developmental toxicity and carcinogenicity data. Limited genotoxicity data and robust dermal irritation and sensitization data were available. After reviewing data on molecular weights, the Panel determined that there likely would be no significant skin penetration of these ingredients. Thus, potential systemic exposure is unlikely and reproductive and developmental toxicity or carciniogenicity data were not necessary to evaluate this group of ingredients.

The Panel discussed the potential effect that methyl glucose would have on glucose metabolism were these ingredients to be absorbed and metabolized. As noted above, however, significant dermal penetration of these ingredients was considered unlikely. While there were no available metabolism data, the complete deesterification of these ingredients to produce methyl glucose was considered highly unlikely. Overall, therefore, any impact of dermal application of these ingredients on glucose metabolism would be very unlikely. The Panel also discussed the apparent uncertainty in the definition of these ingredients as with respect to the extent of esterification. Are they mono-, di-, tri-, or tetra-esters or mixtures thereof? Additional data would be useful to document the extent of esterification that would result from the process of manufacturing these esters.

Modified terephthalate polymers

The CIR Expert Panel issued a tentative safety assessment for public comment for the 6 modified terephthalate polymers listed below with the conclusion that they are safe for use in cosmetics in the present practices of use and concentration.

adipic acid/1,4 butanediol/terephthalate copolymer
polybutylene terephthalate
polyethylene isoterephthalate
polyethylene terephthalate
polypentaerythrityl terephthalate
polypropylene terephthalate.

These reportedly function primarily as exfoliants, bulking agents, hair fixatives, and viscosity increasing agents-nonaqueous. While ethylene/sodium sulfoisophthalate/terephthalate copolymer originally was included in this group, the Panel concluded that this ingredient would have different surface properties than the rest of the ingredients and that it was appropriate to exclude this ingredient from this safety assessment.

Polyethylene terephthalate (PET) is approved for use in medical devices (i.e., surgical sutures, esophageal dilators, and surgical mesh). The Panel considers it likely that cosmetic grade PET would be similar to medical grade PET, in terms of the methods of manufacture, impurities, etc.

There was a concern brought to the Panel's attention that PET, in the form of glitter, could cause physical damage to the cornea if it became imbedded in the eye. In 1985, for example, one company withdrew a glitter product sold as a costume accessory, which may or may not have been intended for use on the face, because of eye injury complaints. However, the available use testing of eye area cosmetic products did not suggest any ocular toxicity and there is a lack of case reports in the literature. Overall, based on the extensive information reviewed by the FDA to support the safety of PET, the Panel concluded that no additional data were needed. In addition, the relatedness of molecular structures, physicochemical properties, and functions and concentrations in cosmetics allow grouping these ingredients together and interpolating the available toxicological data to support the safety of the entire group.

Nylon Polymers

The CIR Expert Panel issued a tentative safety assessment for public comment with the conclusion that the 8 nylon polymers listed below are safe in the present practices of use and concentration in cosmetics.

nylon-6	nylon-10/10	nylon 6/12	nylon-611
nylon-11	nylon-12	nylon-66	nylon-12/6/66

Additional data were submitted that fulfilled data needs concerning irritation and sensitization of nylon ingredients and genotoxicity data on the monomers of nylon ingredients. Concern was expressed that residual monomer data were not available. The Expert Panel reviewed human repeat insult patch test data on nylon-12 at its maximum use concentration of 35%. No sensitization or irritation was observed in this study. From these data, the Panel determined that, whatever residual monomers may be present in nylon-12, were not present at a sufficient level to cause any reactions in test subjects at the maximum use concentration.

Talc

The CIR Expert Panel issued a tentative safety assessment for public comment with the conclusion that talc is safe for use as a cosmetic ingredient in the present practices of use and concentration described in the safety assessment. The Panel did state that talc should not be applied to skin when the epidermal barrier is ulcerated or removed.

The Panel noted that although numerous studies have been performed to examine whether there is a correlation between ovarian cancer and talc, the data do not suggest that application of talc to the perineal area results in migration to the ovaries. Therefore, the Panel did not think there was a causal relationship between ovarian cancer and the cosmetic use of talc. The Panel also discussed the results of positive findings in inhalation carcinogenicity studies of talc. The Panel agreed that the positive findings in these studies are best interpreted as the result of pulmonary overloading , and not relevant to the exposure levels that can reasonably be expected from the use of cosmetic products containing talc. Additionally, the Panel noted that co-carcinogenicity studies in hamsters in which talc was administered intratracheally with benzo[a]pyrene B[a]P, were not relevant to assessing the safety of talc as used in cosmetics.

The Panel agreed that early analyses of the composition of talc in which asbestiform fibers were detected may not be relevant to the current composition of cosmetic talc, because such information was developed before asbestos-free specifications for talc were developed by the cosmetics industry and unreliable analytical methods may have been used. Limited, recent FDA test data confirmed the absence of such fibers. A talc manufacturer representative reported that adequate analytical methods were in place to determine the presence of asbestiform fibers and that suppliers comply with current talc specifications. The industry representative agreed to submit test protocol information and sample certification sheets.

Finally, the Panel added the caveat regarding use of talc in products that could be applied when the epidermal barrier is ulcerated or removed because of case reports of granuloma formation when talc was applied to areas of the skin where the epidermal barrier was not intact.

Insufficient Data Announcement

For this insufficient data announcement, 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, posted on the CIR website, and are available at the CIR office for review by any interested party. ***Please submit data and/or comments to CIR by February 18, 2013, or sooner if possible.*** *This report is scheduled for review by the CIR Expert Panel at its* ***March 18-19, 2013 meeting****.*

Plant and Animal-Derived Amino Acids and Hydrolyzed Proteins

The CIR Expert Panel requested additional data to support the safety of 75 plant- and animal-derived amino acids and hydrolyzed proteins.

The additional data needed are: (1) method of manufacturing data for both plant and animal-derived amino acids and hydrolyzed proteins, especially for hydrolyzed wheat protein; and (2) composition and characterization specifications of plant and animal-derived amino acids and hydrolyzed proteins, including molecular structure and molecular weight ranges from several suppliers to determine if there is a consistency in cosmetic grade plant and animal-derived hydrolyzed proteins, especially hydrolyzed wheat protein.

These ingredients were presented to the Panel in two separate reports, one on source amino acids and one on hydrolyzed source proteins. The Panel decided to combine these 2 reports and title the single report "plant and animal-derived amino acids and hydrolyzed proteins." While data are sought for method(s) of manufacture, it appears that the approaches used to prepare source amino acids and hydrolyzed source proteins would be fundamentally similar, and that the only real difference in the products would be the extent of hydrolysis – either all the way to individual amino acids with potentially some short proteins present, or hydrolysis to short proteins of undetermined or unspecified lengths.

The Panel decided to remove the ingredient hydrolyzed spinal protein from review because spinal-derived ingredients are prohibited by Federal Regulation 21 CFR 700.27.

The 75 ingredients included in this safety assessment are:

Hydrolyzed Proteins:
ammonium hydrolyzed collagen
calcium hydrolyzed collagen
hydrolyzed actin
hydrolyzed albumen
hydrolyzed amaranth protein
hydrolyzed avocado protein
hydrolyzed barley protein
hydrolyzed brazil nut protein
hydrolyzed casein
hydrolyzed conalbumin
hydrolyzed conchiolin protein
hydrolyzed cottonseed protein
hydrolyzed egg protein
hydrolyzed elastin
hydrolyzed extensin
hydrolyzed fibroin
hydrolyzed fibronectin
hydrolyzed gadidae protein
hydrolyzed gelatin
hydrolyzed hair keratin
hydrolyzed hazelnut protein
hydrolyzed hemoglobin
hydrolyzed hemp seed protein
hydrolyzed honey protein
hydrolyzed jojoba protein
hydrolyzed keratin
hydrolyzed lactalbumin
hydrolyzed lupine protein
hydrolyzed maple sycamore protein
hydrolyzed milk protein
hydrolyzed oat protein
hydrolyzed pea protein
hydrolyzed potato protein
hydrolyzed reticulin
hydrolyzed royal jelly protein
hydrolyzed sericin
hydrolyzed serum protein
hydrolyzed sesame protein
hydrolyzed silk
hydrolyzed soy protein
hydrolyzed soymilk protein
hydrolyzed spongin
hydrolyzed sweet almond protein
hydrolyzed vegetable protein
hydrolyzed wheat gluten
hydrolyzed wheat protein
hydrolyzed whey protein
hydrolyzed yeast protein
hydrolyzed yogurt protein
hydrolyzed zein
MEA-hydrolyzed collagen
MEA-hydrolyzed silk
sodium hydrolyzed casein
zinc hydrolyzed collagen

Amino Acids:
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

Re-review and New Data

2-Amino-6-Chloro-4-Nitrophenol – not reopened

The CIR Expert Panel reaffirmed the original conclusion that 2-amino-6-chloro-4-nitrophenol and its hydrochloride salt are safe for use in hair dye formulations at concentrations up to 2.0%.

New toxicokinetics, genotoxicity, skin sensitization, and phototoxicity and photoallergenicity studies and a margin of safety calculation were available and presented to the Panel for review, as were updated concentration of data indicating that the maximum use concentration is now 1.5%. The Panel reviewed the new data and determined to not re-open the safety assessment. The Panel did note that although carcinogenicity data were not available, 2-amino-6-chloro-4-nitrophenol is not significantly absorbed through the skin and is not genotoxic.

m-Phenylenediamine and m-Phenylenediamine Sulfate – not reopened

The CIR Expert Panel reaffirmed the original conclusion that phenylenediamine and m-phenylenediamine sulfate are safe for use in hair dyes at concentrations up to 10%.

According to the European Union Cosmetics Directive, m-phenylenediamine and its salts are among the substances that must not form part of the composition of cosmetic products marketed in the European Union. The Council explained that this language should not be interpreted as a ban, but simply as a natural consequence of an industry decision to not support the safety of phenylenediamine and m-phenylenediamine sulfate as hair dye ingredients in Europe.

The Panel acknowledged that the 10% concentration limit is higher than the maximum use concentrations recently provided by the cosmetics industry from 0.01% to 0.2% for m-phenylenediamine and 1% for m-phenylenediamine sulfate. However, the Expert Panel noted that the 10% limit was based on skin irritation and sensitization test data and does not need to be changed. The CIR Expert Panel determined that there were no new data sufficient to warrant reopening this safety assessment.

PEGs Cocamine - reopened

The CIR Expert Panel reviewed newly provided data and determined to reopen this safety assessment and add 41 ingredients, bringing the total number of ingredients in the report to 47.

In 1999, the CIR Expert Panel concluded that the available data were insufficient to support the safety of PEGs cocamine (PEG-2, -3, -5, -10, -15, and -20 cocamine). The Personal Care Products Council's CIR Science and Support Committee submitted data and analyses relating to these PEGs Cocamine ingredients. This extensive package included: (1) the American Chemistry Council's Fatty Nitrogen Derivatives Panel - Amines Task Group assessment of data availability for the fatty nitrogen derived amines category, including robust summaries for reliable studies; (2) the EPA's human health risk assessment supporting the proposed exemption of alkyl amine polyalkoxylates from the requirement of a tolerance when used as inert ingredients in pesticide formulations; (3) the EPA's human health risk assessment supporting the proposed exemption of *phosphate ester, tallowamine, ethoxylated* from the requirement of a tolerance when used as an inert ingredient in pesticide formulations; (4) a poster presentation on read-across and computer-based analysis to support the safety of PEGs cocamine in cosmetics; and (5) current use concentration data.

There are 3 additional PEGs Cocamine that now are identified as cosmetic ingredients (PEG-4, -8, and -12 Cocamine). Also, other PEG fatty acid amines, which differ from thePEGs Cocamine group only by length of alkyl chain and degree of saturation, may be included. These are:

PEG-2, -7, -11, -15, -20, -22, -25 and -30 tallow amine
PEG-2, -5, -8, -10, -15, -20, -30, -40, and -50 hydrogenated tallow amine
PEG-2 lauramine
PEG-2, -5, -6, -10, -15, -20, -25, and -30 oleamine
PEG-12 palmitamine
PEG-2 rapseedamine
PEG-2, -5, -8, -10, and -15 soyamine
PEG-2, -5, -10, -15, and -50 stearamine

Phthalates – not reopened

The CIR Expert Panel reviewed 3 new studies on phthalates and determined to not reopen the safety assessments of dimethyl, diethyl, or diethyl phthalate, or butyl benzyl phthalate. The conclusion for these ingredients remains that they are safe in cosmetics in the present practices of use and concentration.

Since these original safety assessments were made, the focus of new phthalate studies has been on the potential for endocrine disruption/reproductive and developmental toxicity. The Panel previously reviewed numerous studies, noting that a feeding study using rodents reported a reproductive/developmental toxicity NOAEL of 331 mg/kg/day, but the Panel determined that a reproductive/developmental toxicity NOAEL of 50 mg/kg/day in a rodent gavage study was the worst case NOAEL. To determine exposure, the Panel summed the estimated exposures from all cosmetic product types reported to contain phthalates at specific levels, and determined that exposure to be 9.13 µg/kg/day. Accordingly, a margin of safety of 5,746 was determined.

One new study of children aged 5 to 9, who were part of a Manhattan-Bronx cohort, revealed detectable, although varied, levels of phthalates in the urine of all 244 study participants. Higher levels of both diethyl phthalate and butyl benzyl phthalate were associated with airway inflammation.

Two new studies addressed diabetes and phthalates. Subjects in one study were 1,015 men and women 70 years of age in Uppsala, Sweden. The samples – one sample per subject – were collected in 2001 – 2004 and analyzed 5 – 8 years later. The four phthalates that were the focus of the study included dimethyl phthalate, diethyl phthalate, diisobutyl phthalate, and diethylhexyl phthalate measured in blood and correlated to measures of insulin resistance and poor insulin secretion in non-diabetic subjects.

In the second diabetes and phthalates study, urinary concentrations of phthalate metabolites measured by the CDC and self-reported diabetes in 2,350 women ages 20 to <80 participating in the NHANES (2001- 2008) were used. The odds ratio for diabetes in women with higher levels of n-butyl phthalate, isobutyl phthalate, benzyl phthalate, 3-carboxypropyl phthalate, and the sum of diethylhexyl phthalate metabolites was greater than the odds ratio for women with the lowest concentrations of these phthalates.

The Panel noted that all of these studies identified associations between phthalate metabolites and either diabetes or airway inflammation. Such studies did not suggest a causal link between phthalates and any adverse outcome. The possibility that phthalate metabolites may impact peroxisome proliferation pathways was suggested in the diabetes studies, but that mechanism is not established as a mode of action. The Panel agreed that that there is a need for further study of the reported association between phthalates exposures and diabetes and to investigate possible causal links.

125th Meeting Notes

Director's Report

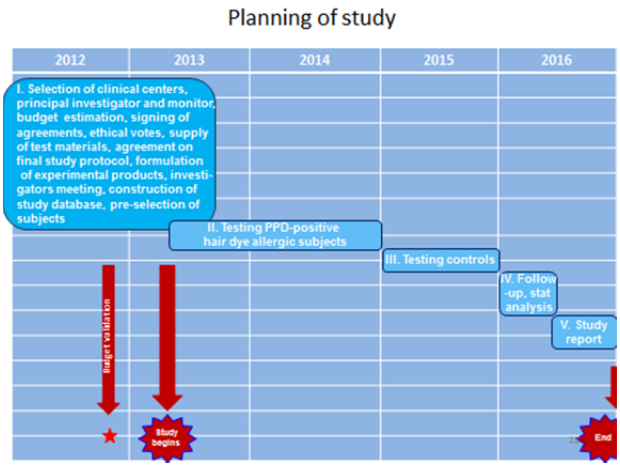
Dr. Andersen congratulated the CIR Expert Panel on a productive year in which some 482 individual cosmetic ingredients were reviewed. This brings the total of number ingredients reviewed by CIR to 3156! That total comprises:

Safe in the present practices of use and concentration – 2060
Safe with qualifications – 982
Insufficient data – 7*
Zero use ingredients – 58
Use in cosmetics not supported – 38
Unsafe – 11

He also remarked on the progress being made to improve the functionality of the CIR website. An outside audit of the website structure reported no fundamental flaws and applauded the efficient use of the drupal database structure to deliver the Panel meeting information to users. Areas for improvement in security and the potential benefits of using of more Drupal capabilities were identified and will be addressed as we upgrade the site to accommodate ingredient searching.

Hair dye self-testing

Dr. Carsten Goebel, Proctor and Gamble, representing the Personal Care Products Council's Hair Coloring Technical Committee (allergy subgroup) reviewed the current status of hair dye self-testing, or, as he termed it, the "allergy alert test." He noted that instructions for such testing are mandatory in the USA, Canada, Japan, Australia, and Brazil, but voluntary in the EU, Latin America, and most Asian countries. Recent reports have suggested that such allergy alert testing may induce allergies to hair dye ingredients.



Dr. Goebel stated that, although it cannot be excluded that an increased application frequency (at a different site) as a result of performing the allergy-alert test may increase the risk of inducing sensitization, the value of the alert test in preventing severe allergic reactions after hair coloring outweighs this potential risk. He asserted that the objective of each allergy-alert test is to prevent severe reactions to an individual hair coloring product in an individual hair-dye user.

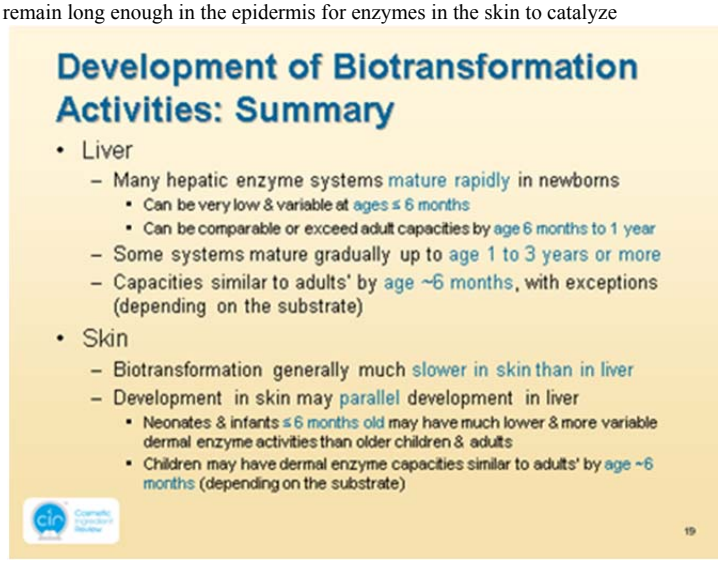
Dr. Goebel described a new effort by the industry to conduct a multicenter proof-of-concept study for the allergy alert test which will address the efficacy of the test under use-like conditions. The study timeline is shown to the left. The study will allow assessment of variations in test parameters, robustness, and independent evaluation by subject/dermatologist.

The CIR Expert Panel noted that hair dyes containing coal tar hair derivatives are exempt from certain adulteration and color additive provisions of the U.S. Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel agreed that there was not a sufficient basis for changing this advice to consumers at this time. The Expert Panel continues to expect that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures, but awaits the data from ongoing investigations by the industry to shed further light on this practice.

Infant skin report

CIR's senior toxicologist, Dr. Ivan Boyer, briefly presented information from a draft overview report on developmental factors that can influence the systemic absorption of topically applied substances through infant skin. CIR staff prepared the draft report as directed by the CIR Expert Panel during their March 2012 meeting.

The draft report addresses two major factors: (1) development of the diffusion barrier of the skin, which is attributed to the stratum corneum; and (2) development of biotransformation enzyme systems in the skin, which can also limit absorption. Dr. Boyer noted that the stratum corneum is an effective semi-permeable barrier at birth, although its effectiveness as a diffusion barrier continues to develop, especially during the first month after birth. He indicated that the skin also has a substantial capacity to metabolize substances that penetrate the stratum corneum, provided that these substances remain long enough in the epidermis for enzymes in the skin to catalyze biotransformation reactions. He noted that there are very little data in the scientific literature specifically addressing the development of biotransformation systems in the skin. However, the information available to characterize development in the liver may be used to support assumptions about the development of biotransformation capacities in the skin.



Dr. Boyer used the slide on the right to emphasize that liver enzyme systems generally develop rapidly after birth, except for enzymes catalyzing glucuronidation reactions. By analogy, the capacities of most biotransformation systems in the skin may be comparable to those in adults by about 6 months of age.

The CIR Expert Panel determined that the draft overview should be developed further as a resource for the Panel and a guide to information that the Panel considers in its safety assessments. They emphasized that a preamble should be included to emphasize that the Panel's purview encompasses cosmetic products intended for use on normal skin, and does not include the use of cosmetic products on preterm infants or infants with skin conditions. They also noted that the normal skin of full-term babies does not appear to have any deficiencies in biotransformation capacities that would warrant concerns that are not already addressed in safety assessments. However, additional information from dermal carcinogenicity animal studies should be incorporated into the document. The Panel also encouraged input from pediatric dermatologists and experts in this field in industry. After receiving comments, the Panel will revisit the overview report.

Report tabled

Achillea millefolium extracts - The CIR Expert Panel tabled further discussion of re-opening this report on ingredients derived from *Achillea millefolium* (aka yarrow) to give industry the opportunity to submit further available irritation and sensitization data at concentrations of use. This safety assessment will be re-opened if data submitted to the CIR satisfy all the data needs listed in the current insufficient data conclusion. Alternatively, a maximum concentration of use may be stated in the conclusion.

The Panel determined that if the report is re-opened, two achillea millefolium-derived ingredients should be added to this safety assessment, but decided that achillea millefolium oil and achillea millefolium flower water were not appropriate to include because of the different characteristics of the oil and because both of these ingredients function only as fragrance ingredients.

The 3 ingredients that are in this safety assessment include: achillea millefolium extract, achillea millefolium flower extract, and achillea millefolium flower/leaf/stem extract. these ingredients function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; and fragrance ingredients.

The Panel noted that irritation/sensitization data were available to support the use of these ingredients at concentrations up to 0.002%, but was not satisfied that the sensitization data were sufficient to address the reported use of these extracts up to 0.04%. The Panel invited the submission of sensitization data for these ingredients at the use concentration of 0.04%. The Panel also noted that an eventual discussion of these achillea millefolium-derived ingredients will mention the presence of photoactive constituents of plant extracts, such a quercetin, but the concentrations of such constituents are low in the achillea-millefolium-derived ingredients and the ingredients themselves are used at low concentrations.

Scientific Literature Reviews

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

Draft reports for these ingredients, along with any unpublished data submitted by interested parties may be presented to the Panel at its meeting on March 18-19, 2013.

In addition, re-reviews of the two safety assessments listed below are scheduled to be considered at the March meeting:

- HC yellow no. 4
- HC orange no. 1

- **These literature reviews are currently in preparation**
  - alkyl PEG=PPG ethers
  - alumina and alumina hydroxide
  - amino acid alkyl amines
  - betaine
  - chamomile ingredients
  - hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl
  - magnesium sulfate
  - phytosterols

Next CIR Expert Panel Meeting - Monday and Tuesday, March 18-19, 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.

►►IMPORTANT CHANGE◄◄

CIR no longer includes an order form listing CIR safety assessments available for sale. Because all CIR documents from this meeting will be posted on the web site, they will be freely available.