

## Cosmetic Ingredient Review Expert Panel 126<sup>th</sup> Meeting (March 18-19, 2013) - Findings

### March 25, 2013

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Cosmetic Ingredient Review [www.cir-safety.org](http://www.cir-safety.org)

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## 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 Unpublished data cited as references in CIR safety assessments are posted on the CIR website and available for review at the CIR office.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](http://www.cir-safety.org).

### Alkyl Esters

The 237 alkyl esters listed below are safe as cosmetic ingredients in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

arachidyl behenate	arachidyl erucate*	chimyl stearate*
arachidyl propionate		coco-caprylate
batyl isostearate*		coco-caprylate/caprato
batyl stearate*		coco-rapeseedate*
behenyl beeswax		decyl castorate*
behenyl behenate		decyl cocoate
behenyl erucate		decyl isostearate*
behenyl isostearate*		decyl jojobate*
behenyl olivate		decyl laurate*
behenyl/isostearyl beeswax*		decyl myristate*
butyl avocadate		decyl oleate
butyl babassuate*		decyl olivate
butyl isostearate*		decyl palmitate*
butyl myristate		decyltetradecyl cetearate*
butyl oleate*		erucyl arachidate*
butyl stearate		erucyl erucate*
butyloctyl beeswax*		erucyl oleate*
butyloctyl behenate*		ethylhexyl adipate/palmitate/stearate*
butyloctyl candelillate*		ethylhexyl C10-40 isoalkyl acidate*
butyloctyl cetearate*		ethylhexyl cocoate
butyloctyl oleate*		ethylhexyl hydroxystearate
butyloctyl palmitate*		ethylhexyl isononanoate
C10-40 isoalkyl acid octyldodecanol esters*		ethylhexyl isopalmitate
C14-30 alkyl beeswax*		ethylhexyl isostearate
C16-36 alkyl stearate*		ethylhexyl laurate
C18-38 alkyl beeswax*		ethylhexyl myristate
C18-38 alkyl c24-54 acid ester*		ethylhexyl neopentanoate*
C20-40 alkyl behenate*		ethylhexyl oleate*
C20-40 alkyl stearate		ethylhexyl olivate
C30-50 alkyl beeswax*		ethylhexyl palmitate
C30-50 alkyl stearate*		ethylhexyl pelargonate
c32-36 isoalkyl stearate*		ethylhexyl stearate
C40-60 alkyl stearate*		heptyl undecylenate
C4-5 isoalkyl cocoate*		heptylundecyl hydroxystearate
caprylyl butyrate*		hexyl isostearate
caprylyl caprylate		hexyl laurate
caprylyl eicosenoate		hexyldecyl hexyldecanoate*
cetearyl behenate		hexyldecyl isostearate
cetearyl candelillate		hexyldecyl laurate
cetearyl isononanoate		hexyldecyl oleate*
cetearyl nonanoate*		hexyldecyl palmitate*
cetearyl olivate		hexyldecyl stearate
cetearyl palmate*		hexyldodecyl/octyldecyl hydroxystearate*
cetearyl palmitate*		hydrogenated castor oil behenyl esters*
cetearyl rice branate*		hydrogenated castor oil cetyl esters*
cetearyl stearate		hydrogenated castor oil stearyl esters*
cetyl babassuate		hydrogenated ethylhexyl olivate
cetyl behenate*		hydrogenated ethylhexyl sesamate*
cetyl caprate		hydrogenated isocetyl olivate*
cetyl caprylate		hydrogenated isopropyl jojobate*
cetyl dimethyloctanoate*		hydroxycetyl isostearate*
cetyl esters		hydroxyoctacosanyl hydroxystearate
cetyl isononanoate*		isoamyl laurate
cetyl laurate		isobutyl myristate*
cetyl myristate		isobutyl palmitate*
cetyl myristoleate*		isobutyl perlargonate*
cetyl oleate*		isobutyl stearate*
cetyl palmitate		isobutyl tallowate*
cetyl ricinoleate		isocetyl behenate*
cetyl stearate		isocetyl isodecanoate*
cetyl tallowate		isocetyl isostearate*
chimyl 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/caprato*
		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 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  
 octyldodecyl 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 isononoate  
 tridecyl laurate\*  
 tridecyl myristate\*  
 tridecyl neopentanoate  
 tridecyl stearate

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

Alkyl esters is the name that CIR devised to describe this large group of cosmetic ingredients, which are reaction products of fatty acids and alcohols. 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 extrapolating the toxicological data to support the safety of the entire group. The 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 data may be extrapolated to support the safety of the entire group. One ingredient originally included in this safety assessment, isopropyl sorbate, was removed because it differs in function and chemical structure from the other ingredients in this group.

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

The Panel also recognized that the potential exists for dermal irritation with the use of products formulated with some of the alkyl esters. Therefore, the Panel specified that products using these ingredients must be formulated to be non-irritating.

#### Alkyl Ethylhexanoates

The 16 alkyl ethylhexanoates listed below are safe as cosmetic ingredients 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 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.

A common concern addressed in the review of the safety of alkyl ethylhexanoates was that 2-ethylhexanoic acid, a possible metabolite, is a liver and developmental toxicant in animal studies at high doses. The mechanism is attributed to a cascade of effects that includes metallothionein (MT) induction followed by zinc accumulation in the liver due to MT binding, and a consequent zinc deficiency in the developing embryo. The Panel determined that results of testing with di-2-ethylhexyl terephthalate (a 2-ethylhexanoic acid precursor used as a model for ethylhexanoic acid exposures that do not induce MT in the liver) suggested that the low rate of metabolic conversion of di-2-ethylhexyl terephthalate follows a time course that allows clearance of the 2-ethylhexanoic acid metabolite before sufficient levels can arise to produce zinc deficiency. The Panel concluded that the low rate of metabolism of alkyl ethylhexanoate compounds that could be absorbed through the skin would not generate 2-ethylhexanoic acid at levels sufficient to trigger the MT-induction-dependent effects observed in animal studies.

The Panel considered that 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

6-Hydroxyindole is safe as a hair dye ingredient in the present practices of use and concentration.

The Panel expressed concern that 6-hydroxyindole appears to be a photosensitizer at a concentration of 5%. Data, however, did not indicate photosensitization at 2%. The Panel noted that this ingredient has 104 uses in hair dye products at concentrations up to 0.5%. The Panel recognized that 6-hydroxyindole is considered a coal tar hair dye. Accordingly, products containing this ingredient 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 concerns about such self-testing, but agreed that following this procedure enables consumers to determine, prospectively, whether they will have an irritation/sensitization reaction, and allow them to avoid subsequent significant exposures. In the future, the Panel will consider the results of ongoing studies by the industry to evaluate the risks and benefits of consumer self-testing.

## Modified terephthalate polymers

The 6 modified terephthalate polymers listed below are safe for use in cosmetics in the present practices of use and concentration.

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

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

These ingredients mostly function as exfoliants, bulking agents, hair fixatives, and viscosity increasing agents-nonaqueous. Polyethylene terephthalate (PET) is used in leave-on products up to 100%.

The Panel considered the presence of a phthalate moiety in these ingredients. Terephthalates incorporate a para-phthalate isomer. This is different from the ortho-phthalate esters (common plasticizers such as di(2-ethylhexyl)phthalate (DEHP)) that have been considered as potential endocrine disruptors. Given the nature of the terephthalates used in cosmetics, there would not be any significant ortho-phthalate impurities in these terephthalate plastics, and no reason that ortho-phthalate esters would be added to them as softeners during manufacturing. The data indicate the absence of endocrine disruption associated with modified terephthalate polymers as used in cosmetics.

The lack of case reports, along with several use tests of eye products containing modified terephthalate polymers up to 46%, led the Panel to conclude that ocular injury from these products is unlikely.

## Nylon Polymers

The 8 nylon polymers listed below are safe in the present practices of use and concentration in cosmetics.

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

\*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.

The Panel considered that unpublished data submitted by the Council supported the conclusion that nylon ingredients in cosmetics would not cause irritation or sensitization. The 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. Likewise, in vitro studies of nylon, as used in cosmetics, found no evidence of genotoxicity. From these data, the Panel determined that residual monomers in nylon-12 were not present, or not released, at concentrations sufficient to cause dermal reactions in subjects tested at the maximum use concentration.

## Talc

Talc is safe in the present practices of use and concentration in cosmetics. The Panel warned that talc should not be used on skin where the epidermal barrier is removed or on skin that has greater than 1st degree burns, because case reports indicate that granulomas formed when talc was applied to skin where the epidermal barrier was not intact.

The Panel received documentation from industry of the analytical methods used to confirm the purity of talc, particularly the absence of asbestos, quartz and other inorganic substances. The Panel also reviewed representative certificates of analysis of talc from two suppliers. Taken together, the information provided sufficient evidence of compliance with the 1976 cosmetics industry specification that talc used in cosmetic products is free of asbestiform fibers.

## Tentative Safety Assessments

*These tentative safety assessments will be posted on the CIR website at [www.cir-safety.org](http://www.cir-safety.org) on or before **March 29, 2013**. Interested persons are given 60 days to comment, provide information and/or request an oral hearing before the CIR Expert Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, 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 **May 10, 2013, or sooner if possible**. These reports may be scheduled for review by the CIR Expert Panel at its **June 10-11, 2013** meeting.*

## Animal- and plant-derived amino acids

The Panel issued a tentative safety assessment for public comment for the 21 animal- and plant-derived amino acids ingredients listed below with the conclusion that they are safe in the present practices of use and concentration as described in the safety assessment.

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

\*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.

The above ingredients had been included in a safety assessment that also included plant- and animal-derived hydrolyzed proteins, but the Panel segregated the amino-acid group and tabled the hydrolyzed-protein group (see 126<sup>th</sup> meeting notes).

The Panel expressed concern about the lack of information regarding method of manufacturing and impurities that may be present in these amino acids derived from plant and animal sources. The Panel considered that vigorous acid hydrolysis would yield amino acids with little or no residual peptides, because such acid hydrolysis attacks all of the peptide bonds in a protein in a non-preferential manner. The Panel was concerned that enzymatic hydrolysis of proteins can disrupt the peptide bonds in a protein in a site-specific manner, and may produce di-, tri- or other peptides, as well as amino acids. Such residual impurities may have the potential to cause allergic reactions in sensitive individuals. Input was sought on the usual methods used to produce amino acids from animal and plant proteins. If the methodology involves rigorous acid hydrolysis, there is less concern that residual small peptides will be present. In any case, the Panel would emphasize that industry should manufacture plant- and animal-derived amino acids in a way that ensures that residual peptides could not cause allergic reactions in sensitive individuals.

### **Boron Nitride**

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

The Panel remarked, however, that irritation and sensitization data were not provided from tests of the maximum reported use concentration (25%) in eye formulations. Because human repeat insult patch test (HRIPT) data were available for 18.7% in formulation, the Panel determined that the data could be considered adequate, although HRIPT data from tests using up to the 25% maximum would be preferable. Further, the available HRIPT study tested only 55 subjects. Thus, additional HRIPT data would greatly improve the basis for the Panel's conclusion.

The Panel also noted that, although there are data gaps, this ingredient is an insoluble polymer that is not expected to penetrate the skin and, even if it did, it would not be expected to cause adverse effects. Although nanoparticles of boron nitride are not reported to be used in cosmetic formulations, the lack of toxicity observed in a single-dose intravenous study of boron nitride nanotubes supports the safety of the other forms of boron nitride that are used in cosmetics. The discussion of the physical/chemical form(s) of boron nitride that are used in cosmetics indicated that further chemical characterization data could clarify their chemical structures and strengthen the safety assessment.

### **Methyl Glucose Polyethers and Esters**

The Panel issued a revised tentative safety assessment for public comment with a conclusion that the 25 methyl glucose polyethers and esters listed below are safe as used in cosmetics in the present practices of use and concentration, except that the available data are insufficient for evaluating the safety of methyl glucose sesquistearate and PEG-20 methyl glucose sesquistearate in lipsticks.

#### Ethers:

methyl glucose caprylate/caprinate\*  
methyl glucose dioleate  
methyl glucose isostearate\*  
methyl glucose laurate\*  
methyl glucose sesquicaprylate/ sesquicaprate\*  
methyl glucose sesquicoate\*  
methyl glucose sesquistearate  
methyl glucose sesquistearate\*  
methyl glucose sesquiolate  
methyl glucose sesquistearate

#### Polyethers

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

#### Esters and polyethers:

PEG-120 methyl glucose dioleate  
PEG-20 methyl glucose distearate  
PEG-80 methyl glucose laurate\*  
PEG-20 methyl glucose sesquicaprylate/ sesquicaprate\*  
PEG-20 methyl glucose sesquiolate\*  
PEG-20 methyl glucose sesquistearate  
PEG-120 methyl glucose triisostearate\*  
PEG-120 methyl glucose trioleate

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

As previously issued, the tentative report on these ingredients indicated that the polyether form of these methyl glucose ingredients reportedly function as skin and hair conditioning agents, whereas the methyl glucose esters and the ester/polyether forms function only as skin conditioning agents in cosmetic products.

Uses of three ingredients in lipsticks raised the concern about repeated ingestion as a route of exposure that Panel had not previously considered. There was, however, some confusion regarding use of these ingredients in lipsticks. Information from FDA's 2013 VCRP database indicated uses of methyl glucose sesquistearate and PEG-20 methyl glucose sesquistearate in lipsticks. Use concentration data were supplied by the Personal Care Products Council for methyl glucose sesquistearate and PEG-20 methyl glucose distearate (not reported in the VCRP) in lipsticks, but no use concentration data were available for PEG-20 methyl glucose sesquistearate. The absence of use concentration data for PEG-20 methyl glucose sesquistearate in lipsticks was particularly concerning because no systemic toxicity data sufficient to support the safety of uses in lipsticks were available. Until such information is available, the Panel determined that the data are insufficient for evaluating the safety of these methyl glucose polyethers and esters in lipsticks.

Use concentration data are needed for PEG-20 methyl glucose sesquistearate in lipsticks (or a determination that this ingredient is not actually used in lipsticks). Regardless, two ingredients clearly are used in lipsticks and, so that the Panel can assess the risks of ingestion, adequate repeated-dose oral toxicity data or other appropriate systemic toxicity data are needed.

### **Nitrocellulose**

The CIR Expert Panel issued a tentative safety assessment for public comment with the conclusion that nitrocellulose and collodion are safe in the present practices of use and concentration.

The Panel debated the need to include collodion in this report. While nitrocellulose is widely used in nail polish and nail enamel, basecoat, and undercoat formulations, no uses of collodion appeared in the VCRP data. It is presumed, however, that there is at least one use of collodion, because a maximum concentration of use in a nail product was reported in response to a survey conducted by the Personal Care Products Council. The Panel considered, therefore, that the tentative report can address collodion as well as nitrocellulose.

Collodion is listed in the International Cosmetic Ingredient Dictionary and Handbook as a cosmetic ingredient. Based on its definition, however, it appeared to the Panel that collodion is a solution of nitrocellulose, ethanol, and ether, which could be termed a trade name mixture rather than a distinct ingredient. Accordingly, the Panel removed the word collodion from the report title.

If the Panel is correct that collodion is simply nitrocellulose in a volatile vehicle, then data supporting the stability of nitrocellulose in that matrix would be useful. If collodion is the de novo product of a manufacturing process, rather than the product of simply dissolving nitrocellulose in ethanol and ether, then data on that method of manufacture would be essential; Otherwise, collodion could be omitted from the conclusion, or require an insufficient data announcement.

The Expert Panel did note that sensitization testing was conducted using a concentration that was less than the maximum reported use concentration. Because most use is in nail care products, significant exposure to the skin would be minimized, so that these data likely are adequate. Also, the high molecular weight and chemical properties preclude significant absorption of this nail formulation ingredient.

## **Re-review and New Data**

### **HC orange no. 1 – not reopened**

The Panel reaffirmed the original conclusion that HC orange no. 1 is safe as a hair dye ingredient at concentrations  $\leq 3\%$ .

The Panel reviewed the evaluation of this hair color ingredient in Europe and noted no new safety issues. The concentration of use for this hair dye has increased from 0.15% to 0.55%, but the use concentration is still well below the maximum concentration of 3% supported by the available data.

The Panel recognized that HC orange no.1 can be considered a coal tar hair dye. Accordingly, products containing this ingredient 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 has considered concerns about such self-testing, but agreed that following this procedure enables consumers to determine, prospectively, whether they will have an irritation/sensitization reaction, and allow them to avoid subsequent significant exposures. In the future, the Panel will consider the results of ongoing studies by the industry to evaluate the risks and benefits of consumer self-testing

### **HC yellow no. 4 – not reopened**

The Panel reaffirmed the original conclusion that HC yellow no.4 is safe for use in hair dyes in the present practices of use and concentration.

The Panel reviewed the evaluation of this hair color ingredient in Europe and noted that this color could be subject to n-nitrosation to form potentially carcinogenic reaction products. Accordingly, the Panel cautioned formulators that HC yellow no. 4 should not be used in formulations where N-nitroso compounds may be formed.

The Panel also considered new studies examining reproductive outcomes in rats dosed with HC yellow no.4. While there was some evidence of reproductive toxicity in these studies using rats, all were oral toxicity studies using high concentrations, and the findings are not relevant to cosmetics uses. HC yellow no.4 is not expected to penetrate the skin in hair coloring usage, so no systemic exposure would occur, and reported use concentration for cosmetics are only 0.75%. These new reproductive toxicity data, therefore, do not suggest a concern for use of HC yellow no.4 in hair coloring. New data showing an absence of sensitization potential at concentrations up to 10% added support that the original safety conclusion was correct.

The Panel recognized that HC yellow no. 4 can be considered a coal tar hair dye. Accordingly, products containing this ingredient 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 has considered concerns about such self-testing, but agreed that following this procedure enables consumers to determine, prospectively, whether they will have an irritation/sensitization reaction, and allow them to avoid subsequent significant exposures. In the future, the Panel will consider the results of ongoing studies by the industry to evaluate the risks and benefits of consumer self-testing

### **Hydroquinone and p-Hydroxyanisole - reopened**

These ingredients were previously reviewed by the Panel in separate reports. A new use of these ingredients, alone or in combination, has been reported in UV-cured nail polish gels, and this use is not addressed in either of the previous safety assessments. The Panel agreed to reopen these safety assessments to address the new usage. Interested parties are encouraged to provide all available data relevant to this new use.

### **Methylisothiazolinone - reopened**

The Panel reviewed newly provided clinical data indicating a higher than expected frequency of individuals who have allergic reactions to the preservative methylisothiazolinone. In some cases, comparative data are available indicating a higher frequency of positive reactions than currently seen with the combination preservative, methylisothiazolinone/methylchlorisothiazolinone. The Panel reopened this safety assessment to gather and evaluate further clinical data. Interested parties are encouraged to provide all available data relevant to this concern about allergic reactions.

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

### **Director's Report**

Dr. Andersen congratulated the Panel on their handling of the review material presented to them solely as PDF and Microsoft Word files. While the move to "going paperless" has been discussed over the past year, he explained that the equipment needed to produce the paper copies was no longer going to be available, and the cost of printing the "books" using an outside vendor was prohibitive. So, CIR "just did it." In addition to making safety assessment decisions, this meeting was a learning experience on the new paperless approach. Projecting the reports on a screen turned out to be unnecessary, because everyone focused on using their laptops instead! Feedback from the audience and the Panel members still will be needed, so that we may improve how we do this in the future.

Dr. Andersen also officially announced that he will retire from CIR effective at the end of June, 2013. Dr. Gill will take over the program and work to develop a plan to address CIR's ongoing staffing needs. Dr. Andersen indicated that he will continue to be available on a consultant basis after he retires.

## Reports Tabled

**Animal- and plant-derived hydrolyzed proteins** - The Panel tabled further discussion on animal- and plant-derived hydrolyzed proteins to allow CIR staff to reorganize the report and to analyze further data from Japan regarding Type I allergic reactions to hydrolyzed wheat protein in a soap product.

These ingredients had been presented in a single report package with animal- and plant-derived amino acids, but the Panel split the amino acid ingredients into their own report (see Tentative Reports).

Among the approaches that have been proposed as alternatives to grouping all hydrolyzed proteins together is to organize the ingredients by plant/animal source. In that scheme, proteins derived from wheat, for example, would be the focus of a group that could include hydrolyzed wheat proteins and hydrolyzed wheat protein derivatives. Ideally, such an approach would facilitate consideration of the concern about hydrolyzed wheat protein in Japan and not dilute the evaluation with other unrelated ingredients.

The other perspective is that, while the parent proteins are from different animal and plant sources, the protein hydrolysates are unlikely to represent novel protein sequences with unique toxicities. In this view, hydrolyzed wheat protein and the Type I allergic reactions reported in Japan are unique to hydrolyzed wheat protein, and are not associated with exposures to hydrolyzed proteins from other sources.

At the time the report was tabled, the 54 ingredients included in this safety assessment were:

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

\*Not reported to be in current use.

**Hypericum perforatum- derived ingredients** - The Panel tabled further discussion of hypericum perforatum-derived ingredients to develop language for the discussion to reflect a growing concern about constituents that may be present in multiple botanical ingredients in cosmetic formulations, resulting in greater than expected exposures to said constituents. For these ingredients, hypericin, a known photosensitizer, might be a good example of such constituents of concern.

The seven ingredients in this amended safety assessment are:

hypericum perforatum extract,	hypericum perforatum flower/twig extract,
hypericum perforatum flower extract,	hypericum perforatum leaf extract, and
hypericum perforatum flower/leaf extract,	hypericum perforatum oil.
hypericum perforatum flower/leaf/stem extract,	

**Palmitoyl oligopeptides** - The report was tabled pending reorganization of this document. These ingredients were preliminarily grouped together, as they are related structurally by an identical fatty, hydrophobic tail connected to a variable sequence of peptides.

The Panel noted, however, that the terminology used for these ingredients does not enable adequate evaluation.

Further information is sought to better understand the extent and manner in which solid-phase peptide synthesis is used to create the peptide portion of such fatty acid peptide ingredients. If additional information enables a better understanding of the amino acid sequences of the peptides of these ingredients than afforded by their definitions in the dictionary, then grouping them together in some fashion may be reasonable.

If there is a substantial degree of randomness associated with the peptides of these ingredients, then it would be important for the Panel to consider how that might influence the safety evaluation. For example, some small peptides are potent stimulators of angiogenesis. The potential for such an activity to promote tumor growth and metastasis in people with undiagnosed skin cancer might then be an issue. Given the present uncertainties, grouping a large number of these ingredients together might be inappropriate.

At the time the report was tabled, the following ingredients were included:

palmitoyl oligopeptide	palmitoyl dipeptide-7
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palmitoyl dipeptide-10  
 palmitoyl dipeptide-13  
 palmitoyl dipeptide-17  
 palmitoyl dipeptide-18  
 palmitoyl tripeptide-1  
 palmitoyl tripeptide-4  
 palmitoyl tripeptide-5  
 palmitoyl tripeptide-8  
 palmitoyl tripeptide-28  
 palmitoyl tripeptide-29  
 palmitoyl tripeptide-31  
 palmitoyl tripeptide-36  
 palmitoyl tripeptide-37  
 palmitoyl tripeptide-38  
 palmitoyl tripeptide-40  
 palmitoyl tripeptide-42  
 palmitoyl tetrapeptide-7  
 palmitoyl tetrapeptide-10  
 palmitoyl tetrapeptide-20  
 palmitoyl pentapeptide-4  
 palmitoyl pentapeptide-5  
 palmitoyl hexapeptide-12

palmitoyl hexapeptide-14  
 palmitoyl hexapeptide-15  
 palmitoyl hexapeptide-19  
 palmitoyl hexapeptide-26  
 palmitoyl hexapeptide-32  
 palmitoyl hexapeptide-36  
 palmitoyl hexapeptide-27 acetate  
 palmitoyl heptapeptide-5  
 palmitoyl nonapeptide-6  
 palmitoyl decapeptide-21  
 palmitoyl oligopeptide-70  
 palmitoyl hydrolyzed collagen  
 palmitoyl hydrolyzed milk protein  
 palmitoyl hydrolyzed wheat protein  
 potassium palmitoyl hydrolyzed corn protein  
 potassium palmitoyl hydrolyzed oat protein  
 potassium palmitoyl hydrolyzed rice protein  
 potassium palmitoyl hydrolyzed sweet almond protein  
 potassium palmitoyl hydrolyzed wheat protein  
 sodium palmitoyl hydrolyzed collagen  
 sodium palmitoyl hydrolyzed wheat protein

**Tromethamine** - The Panel tabled the safety assessment of tromethamine so that aminomethyl propanediol (AMPD) and aminoethyl propanediol (AEPD) may be incorporated into the report.

The Panel noted that there were no sensitization data for tromethamine and that it is used up to 4% in both leave-on and rinse-off products. The only available sensitization data is for AEPD up to 0.5%. It was also noted that impurity data were lacking. The Panel invites additional sensitization data at the maximum use concentration and data on impurities. If such data are not submitted, the CIR Expert Panel may issue an insufficient data announcement or a maximum concentration of use may be specified in the conclusion of a tentative report posted for public comment in the future.

#### Draft 2014 Ingredient Review Priorities

Interested parties are invited to comment on the inclusion of the ingredients listed below as 2014 CIR priorities based on those unreviewed ingredients with the largest number of 2013 VCRP uses. Comment also is sought on the additional ingredients that might be included in each ingredient family. Note that the first three are grouped together in anticipation that they would be evaluated as a group. It is likely that not all of those listed will be chosen for work in 2014.

Ingredient	Number of formulations containing ingredient
sodium hydroxide	3961
potassium hydroxide	1032
ammonium hydroxide	946
algae extract	805
ginkgo biloba leaf extract	530
phospholipids	527
sodium benzotriazolyl butylphenol sulfonate	473
sodium methylparaben	466
ethylene/propylene/styrene copolymer	449
avena sativa (oat) kernel extract	444
polysilicone-2	442
butylene/ethylene/styrene copolymer	435
centella asiatica extract	420
buteth-3	409
PEG-150 pentaerythrityl tetrastearate	408
cetyl PEG/PPG-10/1 dimethicone	387
malus domestica (apple) fruit extract	382
potassium cetyl phosphate	377

butyrospermum parkii (shea) butter extract	363
hydrofluorocarbon 152a	360
triethoxycaprylylsilane	354
tridecyl trimellitate	353
panthenyl ethyl ether	351
to be determined hair dye	na

## 2014 Re-reviews

While there is no requirement for CIR to publish an annual list of scheduled re-reviews, below is the list of the potential re-reviews for 2014. This list is based on those safety assessments completed in 1999 or earlier, and not yet re-reviewed. The need for re-review of one or more of these ingredients may already have been addressed, met by other efforts already underway (e.g. PEG-5 cocamine), or planned for 2014.

### Ingredient

glyceryl stearate  
 polysorbate 20  
 ascorbyl palmitate  
 polysorbate 60  
 sodium PCA  
 glyceryl stearate se  
 bisabolol  
 sorbitan stearate  
 polysorbate 80  
 erythorbic acid  
 PEG-7 glyceryl cocoate  
 PEG-150 distearate  
 propylene glycol dicaprylate/dicaprate  
 sodium lactate  
 azulene  
 hydroxystearic acid  
 isostearamidopropyl morpholine lactate  
 nonoxynol-4  
 PEG-5 cocamine  
 PEG-20 hydrogenated lanolin  
 PPG-9 diethylmonium chloride

## Scientific Literature Reviews

- These literature reviews are currently posted on the CIR website at <http://www.cir-safety.org/ingredients/glossary/all>
  - o amino acid alkyl amides
  - o alumina
  - o hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl
  - o alkyl PEG-PPG ethers
  - o *Chamomilla recutita*-derived ingredients

Draft reports for these ingredients, along with any unpublished data submitted by interested parties may be presented to the Panel at its meeting on June 10-11, 2013.

In addition, re-reviews of the safety assessment listed below may be considered at the June 2013 meeting:

- o dioctyl sodium sulfosuccinate
- o polyvinylpyrrolidone
- These literature reviews are currently in preparation
 

o betaine	o pentaerythrityl tetra-di-t-butyl hydroxyhydrocinnamate
o camellia sinensis leaf	o phytosterols
o citrus limon (lemon) fruit	o plant polysaccharide gums (maltodextrin, etc.)
o hydrogenated polydecene	o rosemarinus officinalis (rosemary) leaf
o magnesium sulfate	o trehalose & glucose

**Next CIR Expert Panel Meeting** - Monday and Tuesday, June 10-11, 2013 at the Madison Hotel, 1177 Fifteenth Street, NW, 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.

### ►►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.*