



Cosmetic  
Ingredient  
Review

# 2012 Annual Report

*Mission: The Cosmetic Ingredient Review thoroughly reviews and assesses the safety of ingredients used in cosmetics in an open, unbiased, and expert manner, and publishes the results in the open, peer-reviewed scientific literature.*

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## EXECUTIVE SUMMARY

### Ingredient findings

- CIR completed 19 safety assessments addressing 470 ingredients as used in cosmetics. CIR re-reviewed and confirmed the safety of 16 additional ingredients in 5 previously reviewed reports.
- CIR determined that there were sufficient new data to reopen the safety assessments of 9 previously reviewed ingredients in 3 reports, and these efforts are underway.
- 38 ingredients were newly designated as ingredients for which use in cosmetics was not supported.

### Reviews rolled over to 2013

- Comment was requested on 8 tentative safety assessments addressing 303 cosmetic ingredients.
- Additional data were requested for a group of 75 ingredients.

### CIR Expert Panel members recognition

- Dr. Wilma Bergfeld was recognized for lifetime achievement in dermatology.
- Dr. Curt Klaassen was recognized for distinguished contributions to toxicology throughout his career.

### SAR

- CIR examined emerging, advanced approaches to chemical structure activity relationship analyses for possible use in evaluating the safety of cosmetic ingredients.
- The ongoing development of such tools by the European COSMOS project, the European Union Joint Research Center, the FDA's Office of Food Additive Safety, Proctor & Gamble, and EPA's National Center for Computational Toxicology was reviewed by representatives from each of those groups.

### Nanotechnology

- FDA updated the CIR Expert Panel on the Agency's points to consider in evaluating cosmetics manufactured using nanotechnology.

### Botanical cosmetic ingredients

- The Personal Care Products Council's CIR Science and Support Committee presented a decision-tree that finished-product manufacturers could use to assess the safety of botanical cosmetic ingredients.

### Hair dye self-testing

- The CIR Expert Panel supported the ongoing need for labeling that advises consumers to perform hair dye self-testing to identify and avoid potential allergic reactions.

### Infant skin

- CIR staff reviewed developmental factors that can influence the systemic absorption of topically applied substances through infant skin. A draft report for public comment 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.

## PREFACE

The Cosmetic Ingredient Review was established in 1976 by the industry trade association (then the Cosmetic, Toiletry, and Fragrance Association, now the Personal Care Products Council), with the support of the U.S. Food and Drug Administration (FDA) and the Consumer Federation of America (CFA). Although funded by the Council, CIR and the review process are independent from the Council and the cosmetics industry.

The CIR Procedures established an Expert Panel to set priorities and review and assess ingredient safety data. The nine CIR Expert Panel voting members are physicians and scientists who have been publicly nominated by consumer, scientific, and medical groups; government agencies; and industry. With participation of liaison representatives from government (FDA), consumers (CFA), and industry (the Council), the CIR Expert Panel creates a unique forum for open discussions on issues affecting public safety.

CIR staff members conduct extensive literature searches, compile data, and prepare draft reports on high-priority ingredients. At each stage of the process, CIR seeks the input of all interested parties during a formal 60-day comment period. After multiple opportunities for public comment and open, public discussion, a final safety assessment is issued.

Recognizing that new information may be available on safety assessments completed years ago, CIR also conducts re-reviews to determine if new information is available.



*Dr. Alan Andersen presents the Director's report at the December 2012 CIR Panel meeting. (l to r) Dr. Lillian Gill, CIR Deputy Director, Dr. Andersen, Stanley Millstein, FDA liaison (from the back), and Dr. Wilma Bergfeld, Chair of the CIR Expert Panel.*

The findings of final safety assessments, re-reviewed safety assessments, etc. are given in the relevant section below. These final reports bring 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 (6 of these ingredients are currently being reconsidered after new data were provided)  
Zero use ingredients – 58  
Use in cosmetics not supported – 38  
Unsafe – 11

CIR identified 38 ingredients, in a newly defined category, for which use in cosmetics is not supported. For these 38 ingredients, the available data were insufficient to make a determination of safety, two years had elapsed without those data being provided, yet the ingredients continued to be used. 2012 also saw progress on examining the utility of structure activity relationship (SAR) analyses as a means to inform safety assessments. Other initiatives included position papers on the role that inhalation toxicity plays for cosmetics safety determinations and the need to consider special factors when evaluating ingredients that may contact infant skin.

CIR safety assessments are made available as monographs and are published in the International Journal of Toxicology. Each year, CIR publishes the CIR Compendium, a comprehensive collection of summary information on all CIR reports. Updates and announcements regarding new ingredient safety assessments can be accessed at the CIR web site at [www.cir-safety.org](http://www.cir-safety.org). Questions or comments can be directed to CIR staff at [cirinfo@cir-safety.org](mailto:cirinfo@cir-safety.org).

F. Alan Andersen, Ph.D.  
Director

Lillian J. Gill, DPA  
Deputy Director

## INSUFFICIENT DATA INGREDIENTS UPDATE

Several years ago, the CIR Expert Panel recommended that ingredients for which there is a reported use in FDA's Voluntary Cosmetic Registration Program (VCRP) and data adequate to resolve the insufficiencies have not been received, should not be used in cosmetics. The CIR Steering Committee drafted a change in the CIR Procedures to implement this recommendation. In 2010, the Personal Care Products Council Board of Directors approved a change in CIR Procedures regarding ingredients for which the CIR Expert Panel has made an insufficient data determination.

Three categories were established:

1. **Zero Reported Uses:** Ingredients for which the available data are insufficient, but there is no reported use under FDA's Voluntary Cosmetics Reporting Program. Because these ingredients are not in use, no further action is needed. Were these ingredients to be used in the future, CIR expects data will be provided to support the safety of these ingredients. This group is separately listed under "findings" on the CIR website and in the CIR Compendium table in the "Z" column.
2. **Insufficient Data or Information:** Ingredients for which the available data are insufficient, and there is a reported use in FDA's VCRP. This group is separately listed under "findings" on the CIR website and in the CIR Compendium table in the "I" column. Because these ingredients remain in use, further action is needed if they remain in use. These ingredients will move to category 3 below after two years have passed and data adequate to resolve the insufficiencies are not received.
3. **Use Not Supported by the Data and Information Submitted to the CIR:** The use of these ingredients, for which there is a reported use in FDA's VCRP and data adequate to resolve the insufficiencies have not been received (within a 2-year period after the insufficient data determination was made), is not supported.

On October 8, 2010, CIR listed the category 3 ingredients and alerted all interested parties that they would have a 2-year window in which to submit needed data. In 2012, that window of opportunity expired and this group is now considered "UNS" or use not supported. The 38 ingredients in this group include:

acacia concinna fruit extract	corylus americana (hazel) seed/nut extract
acacia decurrens extract	corylus avellana (hazel) leaf extract
acacia farnesiana flower/stem extract	glyceryl arachidonate
acacia farnesiana flower wax	human placental protein
acacia senegal extract	hydrolyzed placental protein
alcohol denat. denatured with brucine, brucine sulfate, and quassin	placental lipids
aldioxa	placental enzymes
aloe arborescens leaf extract	placental proteins
aloe arborescens leaf juice	juniperus communis fruit extract
aloe arborescens leaf protoplasts	juniperus oxycedrus tar
aloe ferox leaf extract	juniperus virginiana wood extract
arachidonic acid	morpholine
arnica montana	pentaerythrityl rosinate
arnica montana flower extract	piper methysticum (aka- kava kava) leaf/root/stem extract
azulene <sup>1</sup>	PPG-9 diethylmonium chloride,
brucine sulfate	PPG-25 diethylmonium chloride
captan	pyrocatechol <sup>2</sup>
cetethyl morpholinium ethosulfate	SD alcohol 40
coal tar	stearamine

<sup>1</sup> this ingredient may not be in use; confusion with guiazulene

<sup>2</sup> unsafe for leave-on products; use not supported for hair dyes

## FINAL SAFETY ASSESSMENTS ISSUED IN 2012

### Alkyl PEG Sulfosuccinates

Disodium laureth sulfosuccinate and the other 17 alkyl PEG sulfosuccinate salts and esters listed below are safe in the present practices of use and concentration when formulated to be non-irritating.

disodium laureth sulfosuccinate	disodium C12-15 pareth sulfosuccinate*
disodium laureth-6 sulfosuccinate	disodium coceth-3 sulfosuccinate*
disodium laureth-9 sulfosuccinate*	disodium laneth-5 sulfosuccinate*
disodium laureth-12 sulfosuccinate*	disodium C12-14 sec-pareth-3 sulfosuccinate*
disodium deceth-5 sulfosuccinate*	disodium C12-14 sec-pareth-5 sulfosuccinate*
disodium deceth-6 sulfosuccinate	disodium C12-14 sec-pareth-7 sulfosuccinate*
magnesium laureth-3 sulfosuccinate*	disodium C12-14 sec-pareth-9 sulfosuccinate*
disodium C12-14 pareth-1 sulfosuccinate*	disodium C12-14 sec-pareth-12 sulfosuccinate*
disodium C12-14 pareth-2 sulfosuccinate	disodium oleth-3 sulfosuccinate*

Were ingredients in this group not in current use (as indicated by \*) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group and that they would be formulated to be non-irritating.

These ingredients share a sulfo-substituted succinic acid core and function mostly as surfactants – cleansing agents in cosmetics. The data available for disodium laureth sulfosuccinate include single-dose and repeated-dose toxicity, genotoxicity and carcinogenicity, and dermal irritation and sensitization. Reproductive and developmental toxicity data were available for laureths. Because of the similarities in chemical structure and in usage in cosmetics, these data can be extended to address the safety of all alkyl PEG sulfosuccinates.

The Panel acknowledged receipt of a material safety data sheet (MSDS) on disodium laureth sulfosuccinate indicating that this ingredient contains 1,4-dioxane at a maximum level of 0.001% and formaldehyde at a maximum level of 0.056%. The cosmetics industry should continue to use the necessary procedures to remove the 1,4-dioxane impurity from the alkyl PEG sulfosuccinates before blending them into cosmetic formulations. While formaldehyde was reported at a maximum of 0.056% as an impurity, the use of disodium laureth sulfosuccinate at concentrations up to 10% in rinse-off products and at concentrations up to 2% in leave-on products would result in formaldehyde levels well below the threshold for any toxicity concerns.

### **$\alpha$ -Amino Acids**

The following 34  $\alpha$ -amino acids and their salts were found safe in the present practices of use and concentration in cosmetics:

alanine	cystine	lysine
arginine	glutamic acid	lysine HCl
arginine HCl	sodium glutamate	methionine
asparagine	glutamine	phenylalanine
aspartic acid	glycine	proline
sodium aspartate*	sodium glycinate	serine
potassium aspartate	calcium glycinate	threonine
dipotassium aspartate*	magnesium glycinate*	tryptophan
calcium aspartate*	histidine	tyrosine
magnesium aspartate	histidine HCl	valine
cysteine	isoleucine	
cysteine HCl	leucine	

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

The CIR Expert Panel noted that glycine (no stereocenter) and the L-amino acids are listed by FDA as Generally Recognized As Safe (GRAS) direct food additives. These ingredients function as hair and skin conditioning agents. The International Cosmetic Dictionary and Handbook does not distinguish among the  $\alpha$ -amino acids used in cosmetics that are L-stereoisomers from those that are D-stereoisomers (or are mixtures of L- and D-stereoisomers). Amino acids with a mixture of the 2 stereoisomers (DL-) have approved uses as food additives according to the USP Food Chemicals Codex. The FDA's VCRP has registered reported uses of the DL-mixtures in addition to L-amino acids in cosmetics. However, no cosmetic uses were reported for  $\alpha$ -amino acids ingredients that are specifically the D-stereoisomers; the  $\alpha$ -D-amino acids most probably are not used because their production is more costly compared to the forms that are used in cosmetics. The Expert Panel does not anticipate that there are significant toxicological differences in cosmetic applications between the 2 stereoisomers.

The Expert Panel considered comments that were provided by the International Glutamate Technical Committee on monosodium glutamate (MSG). The Panel reiterated that while some individuals may have MSG symptom complex after ingestion of large amounts of MSG in some foods, the low concentrations of MSG in cosmetic products would not be significantly absorbed through topical application or incidental ingestion, and thus, would not cause systemic reactions even in these individuals.

### **Ammonium Hectorites**

Disteardimonium hectorite and the other 3 ammonium hectorite ingredients listed below are safe in the present practices of use and concentration in cosmetic products.

dihydrogenated tallow benzylmonium hectorite\*      stearalkonium hectorite      quaternium-18 hectorite

Were dihydrogenated tallow benzylmonium hectorite, which is not in current use (as indicated by\*), to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in the group.

These clay-based ingredients function as suspending agents in cosmetic products and may be used as viscosity increasing agents (i.e., they thicken the formulation). The CIR Expert Panel reviewed the available single-dose and repeated-dose toxicity data, along with specific studies addressing dermal irritation and sensitization, and determined that the data support the safety of these ingredients in cosmetics. While no data were available on dermal penetration, the Panel viewed these large sheets of octahedral magnesium/lithium silicate, to which are adhered cationic surfactants (e.g., stearalkonium), as unlikely to pass the stratum corneum. Components, such as lithium, in these ingredients are tightly bound and will not leach from these compounds.

## Bis-Diglyceryl Polyacyladipate-1 and Bis-Diglyceryl Polyacyladipate-2

Bis-diglyceryl polyacyladipate-1 and bis-diglyceryl polyacyladipate-2 were found safe in the present practices of use and concentration in cosmetics.

These ingredients are mixed fatty acid esters and different structural configurations are possible within each bis-diglyceryl polyacyladipate ingredient. They are used in cosmetics as lanolin substitutes. The Panel primarily relied on unpublished data submitted by industry. Although gaps remained regarding toxicokinetics and carcinogenicity data, both ingredients are large, highly lipid-soluble compounds that are not expected to efficiently pass through the stratum corneum of the skin. In addition, the fatty acids that comprise these mixed fatty acid esters have separately been determined to be safe for use in cosmetics, which supports the Panel's findings.

## Borosilicate Glasses

The following 5 borosilicate glasses were found safe in the present practices of use and concentration in cosmetics:

calcium sodium borosilicate  
calcium aluminum borosilicate

calcium titanium borosilicate  
silver borosilicate\*

zinc borosilicate\*

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

These ingredients function as bulking agents in cosmetics and are used at concentrations up to 97%. While there is a lack of data on toxicokinetics and repeated dose toxicity, these ingredients are large, stable molecules that are not water soluble, would not penetrate the skin and, therefore, would not be associated with systemic toxicity. They are not dermal irritants or sensitizers.

## Chlorphenesin

Chlorphenesin was found safe in the present practices of use and concentration in cosmetics.

This ingredient is a widely used cosmetic biocide. Some confusion is apparent because a drug, chlorphenesin carbamate (CAS No. 886-754-8) is also frequently called "chlorphenesin." The drug chlorphenesin carbamate has muscle relaxant activity, can depress the central nervous system, and should not be used in cosmetics. The cosmetic ingredient, chlorphenesin (CAS No. 104-29-0), does not have similar activity, based upon published studies. The Panel agreed that the possible confusion of chlorphenesin with chlorphenesin carbamate should be emphasized to help clearly convey that muscle relaxant effects do not appear to be associated with the cosmetic ingredient, chlorphenesin.

## Citric Acid Group

Citric acid, its 12 inorganic salts, and its 20 alkyl esters listed below (total of 33 ingredients) are safe in the present practices of use and concentration.

### *Inorganic Salts*

aluminum citrate  
calcium citrate\*  
copper citrate\*  
diammonium citrate  
disodium cupric citrate\*  
ferric citrate  
magnesium citrate  
manganese citrate\*  
monosodium citrate  
potassium citrate  
sodium citrate  
zinc citrate

### *Alkyl Mono-, Di-, and Triesters*

dilauryl citrate  
distearyl citrate\*  
ethyl citrates  
isodecyl citrate  
isopropyl citrate\*  
stearyl citrate  
tributyl citrate  
tri-C 12-13 alkyl citrate  
tri-C14-15 alkyl citrate  
tricaprylyl citrate  
triethyl citrate  
triethylhexyl citrate

trihexyldecyl citrate\*  
triosocetyl citrate  
triisopropyl citrate\*  
triisostearyl citrate  
trilauryl citrate\*  
trioctyldecyl citrate  
trioleyl citrate\*  
tristearyl citrate\*

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

The focus of this safety assessment was on the dermal exposure to these cosmetic ingredients. The available repeated insult patch test data at the highest leave-on concentration of 4% citric acid demonstrated an absence of both dermal irritation and sensitization, suggesting that these ingredients would not be irritants or sensitizers in formulation. Similarities in chemical structures, physicochemical properties, and functions and concentrations in cosmetics were cited as support for including all 33 ingredients in this safety assessment, and for extending the available toxicological data to support the safety of the entire group.

## Cucumis Sativus (Cucumber) Ingredients

The following six Cucumis sativus (cucumber)-derived ingredients were found safe in the present practices of use and concentration in cosmetics.

cucumis sativus (cucumber) fruit extract  
cucumis sativus (cucumber) extract  
cucumis sativus (cucumber) fruit

cucumis sativus (cucumber) fruit water  
cucumis sativus (cucumber) juice  
cucumis sativus (cucumber) seed extract

As cucumber is a commonly consumed food, these ingredients pose no significant safety issue following oral exposure. Therefore, the CIR Expert Panel focused on the dermal exposure to the low concentrations of these ingredients as used in cosmetics. Available safety test data demonstrated that these ingredients are neither significant dermal irritants nor sensitizers. Cucumbers, and ingredients derived from cucumbers, contain a variety of phytosterols, all present at relatively low concentrations. Whereas certain components of these extracts (e.g., isoflavones), could exert significant biological effects were they present at high concentrations, the low levels preclude significant effects. In the Panel's experience reviewing other botanical ingredients, phytosterols and phytosterol esters are not significantly absorbed through the skin and do not result in systemic exposure.

### Dialkyl Malates

The following 6 dialkyl malates were found safe in the current practices of use and concentration in cosmetics:

dibutyl octyl malate\*  
di-C12-13 alkyl malate  
diethylhexyl malate

diisoamyl malate\*  
diisostearyl malate  
dioctyl dodecyl malate\*

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

These ingredients have general functionality in cosmetics as skin conditioning agents and are used at concentrations up to 82%. While complete toxicological data were not available for each of the ingredients, the data that were available indicated that dialkyl malates were not systemic toxicants and were not genotoxic, irritating, or sensitizing in mammalian and/or human studies. These data could be extrapolated to support the safety of the entire group.



*In her role as industry liaison to the CIR Expert Panel, the Council's Dr. Halyna Breslawec, makes a point during the discussion at the Panel meeting – (l to r) Panel members Dr. Daniel Liebler, Dr. James Marks, team leader, Dr. Tom Slaga, Dr. Ron Shank, Dr. Ron Hill, Dr. Breslawec, and Dr. Jay Ansell, the Council.*



## Dimethicone Crosspolymers

The following 62 dimethicone crosspolymers were found safe in the present practices of use and concentration in cosmetics:

acrylates/bis-hydroxypropyl dimethicone crosspolymer\*  
 behenyl dimethicone/bis-vinyldimethicone crosspolymer  
 bis-phenylisopropyl phenylisopropyl dimethicone/vinyl dimethicone crosspolymer\*  
 bis-vinyldimethicone/bis-isobutyl PPG-20 crosspolymer\*  
 bis-vinyldimethicone crosspolymer\*  
 bis-vinyldimethicone/ PEG-10 dimethicone crosspolymer\*  
 bis-vinyldimethicone/PPG-20 crosspolymer\*  
 butyldimethicone methacrylate/methyl methacrylate crosspolymer\*  
 C30-45 alkyl cetearyl dimethicone crosspolymer  
 C4-24 alkyl dimethicone/ divinyl dimethicone crosspolymer  
 C30-45 alkyl dimethicone/ polycyclohexene oxide crosspolymer  
 cetearyl dimethicone crosspolymer  
 cetearyl dimethicone/vinyl dimethicone crosspolymer  
 cetyl dimethicone/bis-vinyldimethicone crosspolymer  
 cetyl hexacosyl dimethicone/bis-vinyldimethicone crosspolymer\*  
 crotonic acid/vinyl C8-12 isoalkyl esters/VA/bis-vinyldimethicone crosspolymer\*  
 dimethicone/bis-isobutyl PPG-20 crosspolymer  
 dimethicone/bis-vinyldimethicone/silsesquioxane crosspolymer\*  
 dimethicone crosspolymer  
 dimethicone crosspolymer-3  
 dimethicone/divinyldimethicone/silsesquioxane crosspolymer  
 dimethicone/lauryl dimethicone/bis-vinyldimethicone crosspolymer\*  
 dimethicone/PEG-10 crosspolymer  
 dimethicone/PEG-10/15 crosspolymer  
 dimethicone/PEG-15 crosspolymer\*  
 dimethicone/phenyl vinyl dimethicone crosspolymer  
 dimethicone/polyglycerin-3 crosspolymer  
 dimethicone/PPG-20 crosspolymer  
 dimethicone/titanate crosspolymer\*  
 dimethicone/vinyl dimethicone crosspolymer  
 dimethicone/vinyltrimethylsiloxysilicate crosspolymer  
 diphenyl dimethicone crosspolymer\*  
 diphenyl dimethicone/vinyl diphenyl dimethicone/silsesquioxane crosspolymer  
 divinyl dimethicone/dimethicone crosspolymer  
 hydroxypropyl dimethicone/polysorbate 20 crosspolymer\*  
 isopropyl titanium triisostearate/triethoxysilylethyl polydimethylsiloxyethyl dimethicone crosspolymer  
 lauryl dimethicone PEG-15 crosspolymer\*  
 lauryl dimethicone/polyglycerin-3 crosspolymer\*  
 lauryl polydimethylsiloxyethyl dimethicone/bis-vinyldimethicone crosspolymer\*  
 PEG-10 dimethicone crosspolymer  
 PEG-12 dimethicone crosspolymer  
 PEG-8 dimethicone/polysorbate 20 crosspolymer\*  
 PEG-12 dimethicone/bis-isobutyl PPG-20 crosspolymer\*  
 PEG-12 dimethicone/PPG-20 crosspolymer\*  
 PEG-10 dimethicone/vinyl dimethicone crosspolymer  
 PEG-10/lauryl dimethicone crosspolymer  
 PEG-15/lauryl dimethicone crosspolymer  
 PEG-15/lauryl polydimethylsiloxyethyl dimethicone crosspolymer\*  
 perfluorononyl dimethicone/methicone/amodimethicone crosspolymer  
 polydimethylsiloxyethyl dimethicone/bis-vinyldimethicone crosspolymer\*  
 polyglyceryl-3/lauryl polydimethylsiloxyethyl dimethicone crosspolymer\*  
 silicone quaternium-16/glycidoxy dimethicone crosspolymer  
 styrene/acrylates/dimethicone acrylate crosspolymer  
 trifluoropropyl dimethicone/PEG-10 crosspolymer\*  
 trifluoropropyl dimethicone/trifluoropropyl divinyl dimethicone crosspolymer\*  
 trifluoropropyl dimethicone/vinyl trifluoropropyl dimethicone/silsesquioxane crosspolymer\*  
 trimethylsiloxysilicate/ dimethicone crosspolymer\*  
 vinyl dimethicone/lauryl/behenyl dimethicone crosspolymer\*  
 vinyl dimethicone/lauryl dimethicone crosspolymer  
 vinyl dimethicone/methicone silsesquioxane crosspolymer  
 vinyl dimethyl/trimethylsiloxysilicate/dimethicone crosspolymer\*  
 vinyl dimethyl/trimethylsiloxysilicate stearyl dimethicone crosspolymer\*

\*Not reported to be in current use. Were the dimethicone crosspolymers 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 the group.

These large, stable, insoluble molecules are used in cosmetics for functions such as bulking and non-aqueous viscosity-increasing agents at concentrations up to 46%. These cosmetic ingredients will not penetrate the skin and cannot cause systemic toxicity. They are neither toxicants in acute toxicity studies, nor are they dermal irritants or sensitizers. A lack of data on possible residual monomer content was noted. For the crosspolymers for which impurities data were available, monomers levels were below the detection limits of the analytical methods used. This suggested to the Panel that steps are taken to remove residual monomers or that residual monomers are contained within the cross-linked structure of these large crosspolymers. The Panel noted that manufacturers should continue to take steps to ensure that monomers and catalysts are at levels as low as reasonably achievable, which would, in turn, suggest that such levels are below the level of toxicological concern.

### Ethanolamides

The 28 ethanolamides listed below are safe in the present practices of use and concentration when formulated to be non-irritating. The Expert Panel cautioned that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

acetamide MEA	oatamide MEA*
azelamide MEA*	oleamide MEA*
babassuamide MEA*	oliveamide MEA*
behenamide MEA*	palm Kernelamide MEA*
C16-22 acid amide MEA*	palmamide MEA*
cocamide MEA	palmitamide MEA*
cocamide Methyl MEA	pantothenamide MEA*
cocamidopropyl betainamide MEA chloride	peanutamide MEA
hydroxystearamide MEA*	ricinoleamide MEA
isostearamide MEA*	stearamide MEA
lactamide MEA	sunfloweramide MEA*
lauramide MEA	tallowamide MEA*
linoleamide MEA*	trideceth-2 Carboxamide MEA
myristamide MEA	undecylenamide MEA

Were ingredients in this group not in current use (as indicated by \*) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group, that they would be formulated to be non-irritating, and that they would not be used in cosmetic products in which N-nitroso compounds may be formed.

Because ethanolamides consist of covalent, secondary amides, the Panel was concerned that secondary amides tend to react with nitrosating agents to form nitrosamides; for this reason that the Panel included the N-nitroso caveat in its conclusion. The Panel noted that if diethanolamine is present as an impurity, the levels of free diethanolamine must not exceed those considered safe by the Panel in the current CIR safety assessment of diethanolamine. Additionally, the Panel reiterated its discussion regarding the positive findings of a dermal carcinogenicity study of diethanolamine, noting that the carcinogenic effects of diethanolamine reported in mice were not thought to be relevant to human exposure from the use of personal care products.

Similarities in chemical structures and cosmetic functions and expected similarities in structure/activity relationships were cited as support for including all 28 ethanolamides in this safety assessment, and for extending the available toxicological data to support the safety of these ethanolamides. The Panel acknowledged the lack of reproductive and developmental toxicity data, but relied on the totality of the data set to demonstrate safety. Supporting this reasoning is the expectation that only very small amounts of these ingredients will be bioavailable.

### Ethanolamine and Ethanolamine Salts

Ethanolamine and the 12 ethanolamine salts listed below are safe in the present practices of use (rinse-off products only) and concentration when formulated to be non-irritating. The Expert Panel cautioned that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

ethanolamine	MEA-laureth-6 carboxylate*	MEA-sulfite*
ethanolamine HCl*	MEA-lauryl sulfate	MEA-tallowate
MEA-benzoate*	MEA-PPG-6-laureth-7 carboxylate*	MEA-undecylenate*
MEA-cocoate	MEA-PPG-8-steareth-7 carboxylate*	
MEA-laureth sulfate	MEA-salicylate*	

Were ingredients in this group not in current use (as indicated by \*) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group, that they would be formulated to be non-irritating, and that they would not be used in cosmetic products in which N-nitroso compounds may be formed.

The CIR Expert Panel noted that the salts dissociate freely in water, and relied on the information available for ethanolamine in conjunction with previous safety assessments of the components of these ingredients. The Panel extrapolated those data to support the safety of the ethanolamine salts in this amended safety assessment.

Because small amounts of diethanolamine could be present in ethanolamine, the Panel was concerned about the levels of free diethanolamine that could be present as an impurity; for this reason the Panel included the N-nitroso caveat in its conclusion. Also, the Panel reiterated its discussion regarding the positive findings of a dermal carcinogenicity study of diethanolamine, noting that the carcinogenic effects of diethanolamine reported in mice were not thought to be relevant to human exposure from the use of personal care products.

### Galactomannans

Guar hydroxypropyltrimonium chloride and the other 15 galactomannans listed below are safe in the present practices of use and concentration.

caesalpinia spinosa gum	hydrolyzed caesalpinia spinosa gum
caesalpinia spinosa hydroxypropyltrimonium chloride*	hydrolyzed guar
carboxymethyl hydroxypropyl guar*	C18-22 hydroxyalkyl hydroxypropyl guar*
cassia gum*	hydroxypropyl guar
cassia hydroxypropyltrimonium chloride	hydroxypropyl guar hydroxypropyltrimonium chloride
ceratonia siliqua gum	locust bean hydroxypropyltrimonium chloride
cyamopsis tetragonoloba (guar) gum	trigonella foenum-graecum hydroxypropyltrimonium chloride*
hydrolyzed ceratonia siliqua gum extract*	

Were ingredients in this group not in current use (as indicated by \*) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group

These ingredients are legume polysaccharides that function mostly as hair/skin conditioning agents and viscosity increasing agents in cosmetic products. The Panel discounted a case report relating to ingestion of curry because the flavor ingredient made from *Trigonella foenum-graecum* that is used in curry is not a galactomannan and, therefore, was not relevant. The Panel also noted that ash from heating guar hydroxypropyltrimonium chloride to high temperatures indicated the presence of inorganic salts as impurities.

### Microbial Polysaccharide Gums

The following 34 microbial polysaccharide gums were found safe in the present practices of use and concentration in cosmetics:

xanthan gum;	sodium carboxymethyl dextran;
hydroxypropyl xanthan gum;*	dextran sulfate;
undecylenoyl xanthan gum;*	sodium dextran sulfate;
dehydroxanthan gum;	sclerotium gum;
xanthan gum crosspolymer;	hydrolyzed sclerotium gum;
xanthan hydroxypropyltrimonium chloride;*	beta-glucan;
gellan gum;	beta-glucan hydroxypropyltrimonium chloride;*
welan gum;*	beta-glucan palmitate;*
biosaccharide gum-1;	hydrolyzed beta-glucan;*
biosaccharide gum-2;	oxidized beta-glucan;*
biosaccharide gum-3;*	sodium carboxymethyl beta-glucan;
biosaccharide gum-4;	pullulan;
biosaccharide gum-5;*	myristoyl pullulan;*
pseudoalteromonas exopolysaccharides;*	levan;*
dextran;	rhizobian gum;
carboxymethyl dextran;*	hydrolyzed rhizobian gum; and
dextran hydroxypropyltrimonium chloride;*	alcaligenes polysaccharides.

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

The Panel noted that although there are some data gaps, the data that are available may be extrapolated to support the safety of the entire group. While there were no specific data on the hydroxypropyltrimonium chloride compounds, data on trimonium ingredients included in the existing safety assessment on trimoniums are applicable for determining the safety of the three hydroxypropyltrimonium chloride compounds included in the present report. The Panel noted that parenterally administered polysaccharides appear to be biotransformed to a limited extent in animal and human studies. However, these very large compounds appear not to be significantly absorbed through the skin and, thus, would have negligible bioavailability. Coupled with a lack of significant toxicity associated with other routes of exposure, the CIR Expert Panel determined that systemic effects were unlikely to result from topical application of cosmetics containing these ingredients.

### Panax spp. Root-Derived Ingredients

The following 13 Panax spp. root-derived ingredients were found safe in the present practices of use and concentration in cosmetics:

hydrolyzed ginseng root*	panax ginseng root oil*
hydrolyzed ginseng root extract	panax ginseng root powder
hydrolyzed ginseng saponins*	panax ginseng root protoplast*
panax ginseng root	panax ginseng root water*
panax ginseng root extract*	panax japonicus root extract*

panax notoginseng root  
panax notoginseng root powder\*

panax quinquefolium root extract

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

These ingredients function in cosmetics mostly as skin conditioning agents at concentrations up to 0.5%. As with many botanical extracts in cosmetics, the potential exists for plant phytosterols to be a constituent. An extensive discussion of the potential estrogenic activity of plant phytosterols has been developed by the Panel in its safety assessment of PEGs soy sterol ingredients. Although no dermal absorption data were available, in the Panel's judgment plant phytosterols and phytosterol esters are not significantly absorbed. Extensive data show that these constituents are not estrogenic, are not reproductive toxicants, are not genotoxic, and are not carcinogenic.

The Panel was aware of a report of pulegone in *Panax quinquefolium* root oil. While the root oil is not a cosmetic ingredient, pulegone toxicity is a concern. Because the extract of other *Panax* spp. root materials may be prepared using a variety of solvents, the Panel considered the possible presence of pulegone in these extracts should be addressed. Accordingly, the Expert Panel alerted finished product manufacturers that pulegone content in any ingredient should be < 1%. If these ingredients are used in combination with peppermint oil or any other ingredient that also contains pulegone, the use concentrations for those ingredients should not contribute to a total pulegone level that could produce toxicity through the use of the finished product.



*CIR Panel member Dr. Daniel Liebler (l) discusses ingredient reviews at the December CIR Expert Panel meeting with (r to l) Dr. Donald Belsito, team leader, Dr. Curt Klaassen, and Dr. Paul Snyder.*

## 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.

### Polyether Lanolins

The following 39 polyether lanolins were found safe in the present practices of use and concentration in cosmetics:

PPG-5 lanolin wax	PEG-50 lanolin
PPG-5 lanolin wax glyceride	PEG-55 lanolin*
PEG-75 lanolin wax*	PEG-60 lanolin
PEG-5 hydrogenated lanolin*	PEG-70 lanolin*
PEG-10 hydrogenated lanolin*	PEG-75 lanolin
PEG-15 hydrogenated lanolin*	PEG-85 lanolin
PEG-20 hydrogenated lanolin	PEG-100 lanolin*
PEG-24 hydrogenated lanolin	PEG-150 lanolin
PEG-30 hydrogenated lanolin*	PEG-75 lanolin oil*
PEG-40 hydrogenated lanolin*	polyglyceryl-2 lanolin alcohol ether*
PEG-70 hydrogenated lanolin*	PPG-2 lanolin alcohol ether*
PEG-5 lanolin	PPG-5 lanolin alcohol ether*
PEG-10 lanolin*	PPG-10 lanolin alcohol ether*
PEG-20 lanolin*	PPG-20 lanolin alcohol ether*
PEG-24 lanolin*	PPG-30 lanolin alcohol ether*
PEG-25 lanolin*	PPG-20-PEG-20 hydrogenated lanolin*
PEG-27 lanolin*	PPG-12-PEG-50 lanolin
PEG-30 lanolin	PPG-12-PEG-65 lanolin oil
PEG-35 lanolin*	PPG-40-PEG-60 lanolin oil*
PEG-40 lanolin	

\*Not reported to be in current use. Were the polyether lanolins 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 the group.

This is an amended safety assessment. Polyether lanolins are used as hair and skin conditioning agents and can function as surfactants/emulsifiers. Data regarding the safety of lanolin itself, acetylated lanolin alcohols, PEGs lanolin, alkyl PEG ethers, propylene glycols, and PEGs were combined with the data previously available for PPG-5 lanolin wax and PPG-5 lanolin wax glyceride to support the safety of the larger group of polyether lanolins.

### Synthetic Fluorophlogopite

Synthetic fluorophlogopite was found safe for use in cosmetics in the present practices of use and concentration.

This mica-like ingredient (picture layer-upon-layer of a clay-like mineral) functions as a bulking agent and a viscosity increasing agent in cosmetics. The CIR Expert Panel reviewed the available single-dose and repeated-dose toxicity data, along with specific studies addressing dermal irritation and sensitization, and determined that the data support the safety of this ingredient in cosmetics. While synthetic fluorophlogopite has the unique feature of fluorine-substituted magnesium/aluminum silicate sheets (fluorine appears to enhance thermal stability), the structure still consists of sheets of clay separated by layers of potassium ions. Because of the essential structural similarity of synthetic fluorophlogopite (with a mica-like layered structure) to other aluminum silicate clays, the data available on 18 individual silicate clays in an earlier safety assessment supported the safety of synthetic fluorophlogopite.

## 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.

## Vitis Vinifera (Grape)-Derived Ingredients

The following 24 *Vitis vinifera* (grape)-derived ingredients were found safe in the present practices of use and concentration in cosmetics:

vitis vinifera (grape);	vitis vinifera (grape) leaf wax;*
vitis vinifera (grape) bud extract;	vitis vinifera (grape) root extract;*
vitis vinifera (grape) flower extract;*	vitis vinifera (grape) seed;
vitis vinifera (grape) fruit extract;	vitis vinifera (grape) seed extract;
vitis vinifera (grape) fruit powder;	vitis vinifera (grape) seed powder;
vitis vinifera (grape) fruit water;	vitis vinifera (grape) shoot extract;*
vitis vinifera (grape) juice;	vitis vinifera (grape) skin extract;*
vitis vinifera (grape) juice extract;	vitis vinifera (grape) skin powder;*
vitis vinifera (grape) leaf extract;	vitis vinifera (grape) vine extract;
vitis vinifera (grape) leaf oil;*	vitis vinifera (grape) vine sap;*
vitis vinifera (grape) leaf/seed/skin extract;*	hydrolyzed grape fruit;*
vitis vinifera (grape) leaf water;*	hydrolyzed grape skin.*

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

Some of the constituents of *Vitis vinifera* plant parts, such as ascorbic acid, biotin, and malic acid, are cosmetic ingredients for which a CIR safety assessment is available. Others are compounds that have been discussed in previous CIR assessments. For example, whole *Vitis vinifera* contains a variety of phytosterols at low concentrations. In previous CIR safety assessments, the Panel has addressed the potential estrogenic and other effects of phytosterols. Although no dermal absorption data were available, in the Panel's judgment, phytosterols and phytosterol esters are not significantly absorbed and do not result in systemic exposure. Additionally, these constituents are not estrogenic, are not reproductive toxicants, are not genotoxic, and are not carcinogenic.

The Panel also noted that the leaf extract, which is used at up to 3% in perfumes, is a highly colored component and could be photoactive. The dermatologists on the Panel remarked that phototoxicity issues have not been reported in vineyard workers, and the Panel relied on its clinical expertise to alleviate the concern of possible phototoxic effects of *vitis vinifera* (grape) leaf extract. The Panel also noted that that low levels of quercetin are present in some components of *Vitis vinifera*. However, because the *Vitis vinifera*-derived ingredients are used at very low concentrations in cosmetics, and because the concentrations of quercetin in the plant parts are low, the presence of quercetin was below the level of toxicological concern.

## RE-REVIEWS IN 2012 – NOT REOPENED

### 2-Amino-6-Chloro-4-Nitrophenol

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 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 noted that, although carcinogenicity data were not available, 2-amino-6-chloro-4-nitrophenol is not significantly absorbed through the skin and is not genotoxic.

## Parabens

The Panel reaffirmed the safety of parabens as preservatives in the present practices of use and concentration in cosmetics.

At the request of the Personal Care Products Council, the Panel re-examined its 2008 published safety assessment of parabens. The Council cited new opinions from the European Commission's Scientific Committee on Consumer Safety (SCCS) regarding (1) safe levels of parabens in cosmetics and (2) parabens in products intended for children under 3 years of age.

The SCCS updated opinion on parabens confirmed that methyl- and ethylparaben are safe up to 0.4% for one and a total of 0.8% for any mixture, but lowered the level in cosmetics considered safe for propyl- and butylparaben to 0.19% for any one or any mixture. This lowering appeared to be based on a re-evaluation of existing dermal penetration/metabolism data, not on new data. The Panel reiterated its very conservative value of 50% dermal penetration and the robust toxicity study it used to estimate a margin of safety. The Panel stated that its published margins of safety are still valid and continue to offer ample assurance that parabens are safe in the present practices of use and concentration.

The second recent SCCS opinion addressed the Danish decision to ban parabens in products intended for children under 3 years of age. The SCCS opinion appeared to indicate that there is no adequate scientific basis for the Danish ban, and the Panel agreed with that position. The SCCS opinion noted that additional data would be useful for children <6 mo. of age.

The Panel agreed that infants are a sensitive subpopulation for risk assessment and has consistently considered the higher skin surface area to body mass ratio in infants when performing cosmetic ingredient safety assessments. The Panel believes that more data regarding dermal penetration through infant skin and potential metabolism in infant skin are available and should be brought to bear on this question. The Panel directed CIR staff to begin the process of pulling that information together in an overview report, with the intent of providing the information to the public..

The Panel also addressed three new studies of parabens. One new study suggesting that the preservative action of parabens might be linked to allergic sensitization, while other potential endocrine disrupting chemicals were not linked to this condition, was considered by the CIR Expert Panel. The Panel also reviewed a study that measured paraben concentrations as a function of location in breast tissue. In addition, an in vitro study of immortalized but untransformed human breast epithelial cells in culture reported that cell transformation occurred at paraben concentrations that were considered to be comparable to the concentrations measured in some of the breast tissue samples studied. The Panel determined that these data are not relevant to the assessment of the safety of parabens in cosmetics. The Panel reaffirmed that parabens are safe in the present practices of use and concentration. The Panel suggested that their extensive discussion about these data would be important to communicate to the public and to the scientific community.

Barr L et al. 2012. Measurement of paraben concentrations in human breast tissue at serial locations across the breast from axilla to sternum. *J. Appl. Toxicol.* 32: 219-232.

Khanna S and Darbre PD. 2012. Parabens enable suspension growth of MCF-10A immortalized, non-transformed human breast epithelial cells. *J. Appl. Toxicol.* [Epub ahead of print].

Savage JH et al. 2012. Urinary levels of triclosan and parabens are associated with aeroallergen and food sensitization. *J Allergy Clin Immunol* 130(2): 453-460.

## m-Phenylenediamine and m-Phenylenediamine Sulfate

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 greater than the maximum use concentrations of 0.01% to 0.2% for m-phenylenediamine and 1% for m-phenylenediamine sulfate recently provided by the cosmetics industry. 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.

## Phthalates

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. The Panel conservatively estimated a reasonable worst-case total exposure from the concurrent use of multiple cosmetic product types reported to contain phthalates 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 there is a need for further study of the reported association between phthalates exposures and diabetes and to investigate possible causal links.

### Triclosan

The CIR Expert Panel determined to not reopen the safety assessment of triclosan. One new study suggesting that the biocide function of triclosan might be linked to allergic sensitization, while other potential endocrine disrupting chemicals were not linked to this condition, was considered by the CIR Expert Panel. In addition, the Panel reviewed a study of the effects of triclosan on muscle excitation-contraction coupling and divalent calcium dynamics in *in vitro* and *in vivo* tests. The data from these studies were not considered relevant to the assessment of the safety of triclosan in cosmetics. The Panel reaffirmed that triclosan is safe for use in cosmetics in the present practices of use and concentration. The Panel suggested that their extensive discussion about these data would be important to communicate to the public and to the scientific community.

Cherednichenko G et al. 2012. Triclosan impairs excitation-contraction coupling and Ca<sup>2+</sup> dynamics in striated muscle. *Proceedings of the National Academy of Sciences* 109(35): 14158-14163.

Savage JH et al. 2012. Urinary levels of triclosan and parabens are associated with aeroallergen and food sensitization. *J Allergy Clin Immunol* 130(2): 453-460.

## RE-REVIEWS IN 2012 – REOPENED

### Formic Acid

The Panel reopened this report to address the new functions reported for this ingredient. Previously, formic acid was described as a pH adjuster only, and the CIR conclusion focused on that use alone (safe when used in cosmetic formulations as a pH adjuster with a 64 ppm limit for the free acid). Now this ingredient is described as a fragrance and a preservative, in addition to the pH adjuster function. The Panel will examine the available safety test data to determine if they support the safety of formic acid for these functions. Interested parties should use this opportunity to provide additional data. Information on the concentration of use associated with each function would be very useful. The Panel also determined to add sodium formate to the reopened safety assessment. Available data for sodium formate should be provided.

### PEGs Cocamine

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 the PEGs 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 rapeseedamine  
 PEG-2, -5, -8, -10, and -15 soyamine  
 PEG-2, -5, -10, -15, and -50 stearamine

## Retinol and Retinyl Palmitate

The CIR Expert Panel determined that there were sufficient new data to warrant reopening this safety assessment and, in particular, to develop a robust review of the available photo co-mutagenicity and photo co-carcinogenicity data. Notable among the available information was a photocarcinogenesis study of retinoic acid and retinyl palmitate conducted by FDA's National Center for Toxicological Research under the auspices of the National Toxicology Program.

CIR will add an additional 7 related ingredients and search for published studies relevant to evaluating their safety as cosmetic ingredients. These additional ingredients include retinyl acetate, retinyl linoleate, retinyl oleate, retinyl propionate, retinyl rice branate, retinyl soyate, and retinyl tallate. Industry is alerted that any available unpublished data on these 7 additional ingredients should be submitted to CIR. Both retinyl palmitate and retinol are widely used cosmetic skin conditioning agents. Retinyl acetate has 27 uses reported to the FDA's Voluntary Cosmetic Registration Program (VCRP), retinyl linoleate has 30 reported uses, and retinyl propionate has 9 reported uses, but the other retinol esters are not reported to be in current use. It will also be important to have current use concentration information for all 9 ingredients.

## END OF YEAR PUBLIC ANNOUNCEMENTS

### Tentative Safety Assessments Issued in December 2012 for Public Comment

*These tentative safety assessments are posted on the CIR website at [www.cir-safety.org](http://www.cir-safety.org). 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*	C20-40 alkyl stearate	cetyl palmitate
arachidyl propionate		C30-50 alkyl beeswax*	cetyl ricinoleate
batyl isostearate*		C30-50 alkyl stearate*	cetyl stearate
batyl stearate*		c32-36 isoalkyl stearate*	cetyl tallowate
behenyl beeswax		C40-60 alkyl stearate*	chimyl isostearate*
behenyl behenate		C4-5 isoalkyl cocoate*	chimyl stearate*
behenyl erucate		caprylyl butyrate*	coco-caprylate
behenyl isostearate*		caprylyl caprylate	coco-caprylate/caprate
behenyl olivate		caprylyl eicosenoate	coco-rapeseedate*
behenyl/isostearyl beeswax*		cetearyl behenate	decyl castorate*
butyl avocadate		cetearyl candelillate	decyl cocoate
butyl babassuate*		cetearyl isononanoate	decyl isostearate*
butyl isostearate*		cetearyl nonanoate*	decyl jojobate*
butyl myristate		cetearyl olivate	decyl laurate*
butyl oleate*		cetearyl palmate*	decyl myristate*
butyl stearate		cetearyl palmitate*	decyl oleate
butyloctyl beeswax*		cetearyl rice branate*	decyl olivate
butyloctyl behenate*		cetearyl stearate	decyl palmitate*
butyloctyl candelillate*		cetyl babassuate	decyltetradecyl cetearate*
butyloctyl cetearate*		cetyl behenate*	erucyl arachidate*
butyloctyl oleate*		cetyl caprate	erucyl erucate*
butyloctyl palmitate*		cetyl caprylate	erucyl oleate*
C10-40 isoalkyl acid octyldodecanol esters*		cetyl dimethyloctanoate*	ethylhexyl adipate/palmitate/stearate*
C14-30 alkyl beeswax*		cetyl esters	ethylhexyl C10-40 isoalkyl acidate*
C16-36 alkyl stearate*		cetyl isononanoate*	ethylhexyl cocoate
C18-38 alkyl beeswax*		cetyl laurate	ethylhexyl hydroxystearate
C18-38 alkyl c24-54 acid ester*		cetyl myristate	ethylhexyl isononanoate
C20-40 alkyl behenate*		cetyl myristoleate*	ethylhexyl isopalmitate
		cetyl oleate*	ethylhexyl isostearate

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

\*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	ethylhexyl ethylhexanoate	myristyl ethylhexanoate*
C12-15 alkyl ethylhexanoate	hexyldecyl ethylhexanoate*	octyldodecyl ethylhexanoate*
C14-18 alkyl ethylhexanoate*	isocetyl ethylhexanoate	stearyl ethylhexanoate
cetearyl ethylhexanoate	isodecyl ethylhexanoate*	tridecyl ethylhexanoate
cetyl ethylhexanoate	isostearyl ethylhexanoate*	
decyltetradecyl ethylhexanoate*	lauryl 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 125<sup>th</sup> 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/twig extract
hypericum perforatum flower extract	hypericum perforatum leaf extract
hypericum perforatum flower/leaf extract	hypericum perforatum oil
hypericum perforatum flower/leaf/stem extract	

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 these ingredients would appropriately include 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:

methyl glucose caprylate/caprinate\*  
methyl glucose dioleate  
methyl glucose isostearate\*  
methyl glucose laurate\*  
methyl glucose sesquicaprylate/ sesquicaprate\*  
methyl glucose sesquicoate\*  
methyl glucose sesquiosostearate  
methyl glucose sesquilaurate\*  
methyl glucose sesquioleate  
methyl glucose sesquisteate

#### 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 disteate  
methyl gluceth-10  
methyl gluceth-20

#### Esters and polyethers:

PEG-120 methyl glucose dioleate  
PEG-20 methyl glucose disteate  
PEG-80 methyl glucose laurate\*  
PEG-20 methyl glucose sesquicaprylate/ sesquicaprate\*  
PEG-20 methyl glucose sesquilaurate\*  
PEG-20 methyl glucose sesquisteate  
PEG-120 methyl glucose triisostearate\*  
PEG-120 methyl glucose trioleate

\*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 carcinogenicity 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 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 stated 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 Issued in December 2012

*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

## New Safety Assessments under Development

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 2013 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
- chamomilla recutita-derived ingredients
- hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl
- magnesium sulfate
- phytosterols

## 2013 REVIEW PRIORITIES

The 2013 Priority list was approved by the CIR Expert Panel. The 15 reports on the list are:

- camellia sinensis leaf extract – 1701 uses
- rosmarinus officinalis (rosemary) leaf extract – 634 uses
- alumina – 612 uses
- pentaerythrityl tetra-di-t-butyl hydroxyhydrocinnamate – 475 uses
- hydrogenated polydecene – 455 uses
- maltodextrin – 442 uses
- trehalose & glucose - 440 & 350 uses, respectively
- betaine – 439 uses
- tocotrienols – 436 uses
- citrus medica limonum (lemon) fruit extract – 421 uses
- PPG-5-ceteth-20 – 414 uses
- phytosterols – 408 uses
- magnesium sulfate – 393 uses
- ceramide 3 – 377 uses
- hydroxypropyl bis(n-hydroxyethyl-p-phenylenediamine) HCl – 75 uses

The list was based on use data from FDA's VCRP, received from FDA in May, 2012. Comments were provided by the Personal Care Products Council's CIR Science and Support Committee. The list includes only the lead ingredients. These lead ingredients, in many cases, will form the nidus for a group. For example, PPG-5 ceteth-20 may be expanded to a group of 160 alkyl PEG/PPG ethers. Magnesium Sulfate may include other inorganic sulfates. As literature reviews and draft reports are prepared for these ingredients, groups may be revised based on the available scientific information. For example certain inorganic sulfates may present different toxicity profiles and be eliminated on that basis. The full list of 2013 priorities will be posted at <http://www.cir-safety.org/about>.

CIR will also re-review safety assessments in 2013. These will include:

- dioctyl sodium sulfosuccinate
- glycolic acid, ammonium, calcium, potassium, and sodium glycolates, methyl, ethyl, propyl, and butyl glycolates, and lactic acid, ammonium, calcium, potassium, sodium, and tea-lactates, methyl, ethyl, isopropyl, and butyl lactates, and lauryl, myristyl, and cetyl lactates
- HC yellow no. 4
- HC orange no. 1
- iodopropynyl butylcarbamate (IPBC)
- polyvinyl alcohol
- polyvinylpyrrolidone (PVP)
- sodium alpha-olefin sulfonates

## PANEL MEMBERS RECOGNIZED

### CIR Expert Panel Chair, Dr. Wilma F. Bergfeld, Receives Master Dermatologist Award

Dr. Wilma F. Bergfeld, MD, FACP, has received the Master Dermatologist Award from the American Academy of Dermatology (AAD). She was formally recognized at the 70th Annual AAD Meeting in San Diego.

The Master Dermatologist Award recognizes an AAD member who has made significant contributions to dermatology and the AAD over his or her career, according to information on the AAD website.

"I'm the first woman to receive this award, which is nice — I was the first woman president of the American Academy of Dermatology and now I'm the first woman to receive the dermatologist's Master Award," explains Dr. Bergfeld. "I cannot express how thrilled I am to be recognized in this manner."

The recipient of the Master Dermatologist Award is nominated by the History Committee and approved by the Board of Directors, according to the AAD website.

"I was absolutely thrilled," Dr. Bergfeld says. "To have peer recognition at this time in my life is fantastic. To be recognized for the work over your career is fantastic, because not everybody gets that recognition, and I just feel very privileged."





## Curt Klaassen Receives Society of Toxicology Merit Award



Curtis D. Klaassen, PhD, DABT, ATS, Distinguished Professor, University of Kansas Medical Center (KUMC), was the recipient of the 2012 SOT Merit Award in recognition of his distinguished contributions to toxicology throughout his career.

Dr. Klaassen's reputation in toxicology research and education has drawn students from all over the world to be trained under his mentorship. Since joining the faculty of KUMC in 1968, he has mentored 121 scientists, including 31 students who received their PhDs and 64 postdoctoral fellows.

Dr. Klaassen has served as editor of the Casarett and Doull's Toxicology textbook for several decades, and inaugural editor of Toxicological Sciences and associate editor for the Journal of Pharmacology and Experimental Therapeutics, two of the most important journals for the fields of toxicology and pharmacology. He has published more than 600 research articles, reviews, and book chapters, and has been ranked in the Top five Most Highly Cited Pharmacologists/Toxicologists in the world for the last decade.

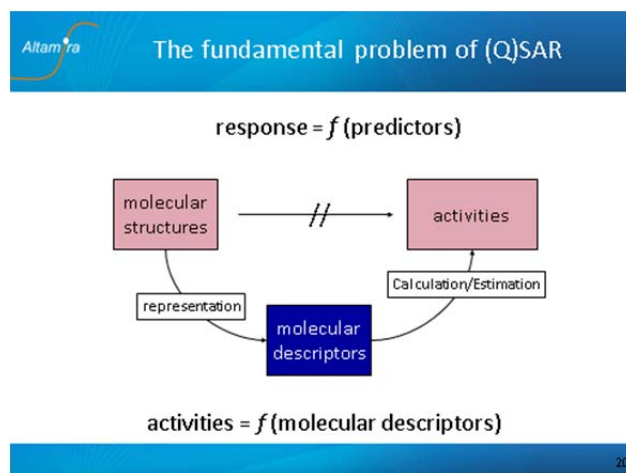
In addition to his remarkably productive contributions to the scientific literature and education of the next generation of toxicologists, Dr. Klaassen has contributed professionally in many other ways. He has been elected to 27 different positions in professional organizations, including President of the Society of Toxicology (1990–1991) and President of IUTOX (1992–1995); he also has served on 75 national/international committees of prominence and as the Chair for the Department of Pharmacology, Toxicology, and Therapeutics at the KUMC (2002–2011). Dr. Klaassen also has participated on numerous panels, including the CIR Expert Panel since 1993.

## PRESENTATIONS AT 2012 CIR EXPERT PANEL MEETINGS

### SAR Workshop

**Chihae Yang, Ph.D.**, is the Chief Scientific Officer of Altamira LLC, which is a knowledge development company collaborating with the U.S. FDA to develop publicly available toxicity databases, and serves as a work package leader for the European COSMOS project. She reviewed the history, development, and prospects of computational toxicology methods and tools, and discussed the current challenges of using these approaches to predict toxicity and support chemical risk assessments.

Dr. Yang explained that computational methods can be used effectively to derive knowledge from theory and the results of past experiments. She illustrated the fundamental problem of quantitative structure activity relationship (Q)SAR analysis, in particular, using this figure. She emphasized that inherent problems and limitations of methods currently being developed must be recognized and addressed before such methods can be widely accepted by the regulatory community and broadly used to support the risk assessment of ingredients in cosmetics or other consumer products.



The central problem is that (Q)SAR technologies cannot predict biological activities directly from molecular structures. Rather, they are used to predict biological activity indirectly, based on molecular descriptors (i.e., electronic and steric/size effects and hydrophobicity) that represent the molecular structures. Further, applying these technologies produces results that need additional transformation and translation to enable using them effectively in risk assessments, which adds more complexity to an already very complex paradigm.

One of the more specific problems to be addressed in the development of these methods is the need for a formal, quantitative, weight-of-evidence approach to synthesizing and presenting the results of structural alert, SAR and read-across analyses. Solving this problem would substantially facilitate the use of these methods to support risk assessments and risk management decisions.

Dr. Yang emphasized that defining mode-of-action (MoA) categories of chemicals will enable the incorporation of mechanistic descriptors, as well as biological assay descriptors, which can significantly improve the interpretability and biological relevance of the results of (Q)SAR analyses. Such (Q)SAR results for chemicals with sufficient data can serve as the basis for developing chemical and biological space profiles. These profiles could, in turn, be used to support reliable read-across for evaluating chemicals for which suitable analogs can be identified, and facilitate the application of knowledge about metabolic pathways, structural alerts, and structure activity relationships to predict toxicological endpoints and potencies for chemicals without adequate data or suitable analogs.

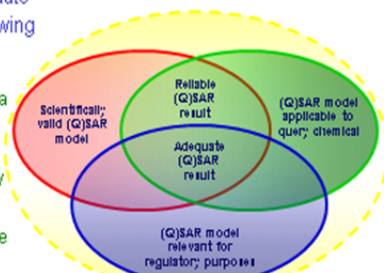
**Andrew Worth, Ph.D.**, is the leader of the Computational Toxicology group at the European Union (EU) Joint Research Centre (JRC) in Ispra, Italy. This group develops and evaluates computational methods for the regulatory assessment of chemicals. Dr. Worth reviewed the EU cosmetic legislation that is largely driving current efforts to develop alternatives to the whole animal testing of cosmetic ingredients, and he discussed the computational tools and approaches that the JRC has developed to help meet that challenge.

Dr. Worth noted that the SEURAT-1 Cluster is a European Commission (EC) research initiative aimed at developing knowledge and technology building blocks required for the ultimate replacement of *in vivo* repeated dose systemic toxicity testing in animals. The objective is to replace such testing with alternative predictive toxicology tools developed based on a complete understanding of how chemicals can cause adverse effects in humans. Within the SEURAT-1 Cluster, the COSMOS project has the goal of developing integrated *in silico* models for predicting the toxicity and supporting the safety assessment of cosmetic ingredients.

### Adequacy of (Q)SAR prediction

In order for a (Q)SAR result to be adequate for a given regulatory purpose, the following conditions must be fulfilled:

- the prediction should be generated by a valid model
- the model should be applicable to the chemical of interest with the necessary level of reliability
- the prediction should be relevant for the regulatory purpose
- adequate and reliable documentation should be provided



#### ECHA guidance on Information Requirements & Chemical Safety Assessment

[http://guidance.echa.europa.eu/docs/guidance\\_document/information\\_requirements\\_en.htm](http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm)

He explained that, while (Q)SAR analyses can replace whole animal testing in principle, it is much more likely that these analyses will be used as a key element of many in integrated toxicology testing strategies.

One of the principle barriers to the acceptance of (Q)SAR methods is the lack of practical guidance on how to use them to support regulatory decisions. Dr. Worth used this diagram to outline three key information elements needed to support the adequacy of (Q)SAR predictions for regulatory purposes.

In addition, petitioners need to explain and document the adequacy of a tool within the appropriate regulatory context if they want to use the tool for this purpose. Standardized templates have been developed for reporting the validity of (Q)SAR models and the adequacy of predictions.

Dr. Worth indicated that acceptable alternatives to whole animal tests should be achievable in the short-term for toxicological

endpoints for which the chemistry is well understood, such as skin irritation, sensitization and penetration, as well as genotoxicity. However, full replacement of whole animal skin sensitization tests is not likely for at least another 7 years, and no timelines have been estimated for more challenging areas, such as toxicokinetics, repeated dose toxicity, carcinogenicity and reproductive toxicity.

He noted that very limited use of *in vitro*, (Q)SAR, and read-across methods have been made under the European REACH regulation to date, probably because the focus has been on evaluating the more dangerous chemicals for which there is much data. Efforts to address lower tonnage chemicals with less information will likely involve the increasing use of (Q)SAR methods, especially grouping and read-across approaches, in accordance with SCCS guidance for the testing and safety assessment of cosmetic ingredients.

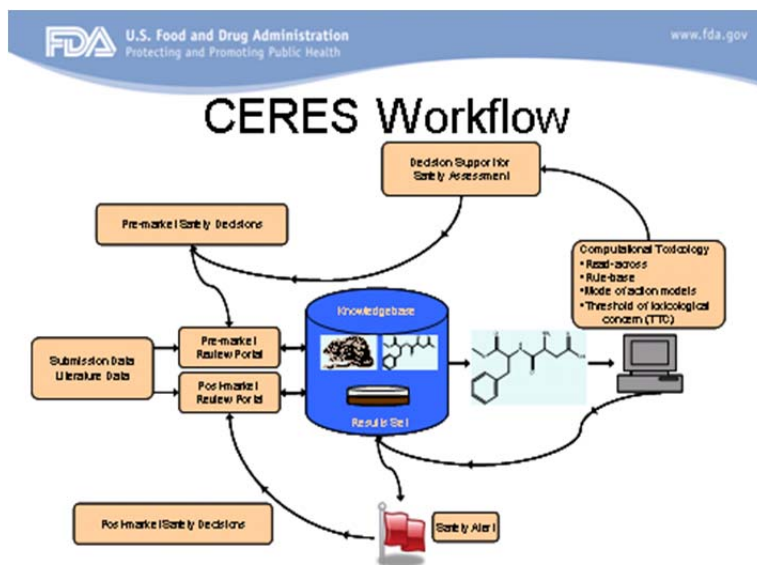
**Kirk Arvidson, Ph.D.**, is a review chemist and leader of the Structure Activity Relationship (SAR) Team in the U.S. FDA Office for Food Additive Safety (OFAS). This team performs computational toxicology modeling and research and knowledgebase development to support the safety assessment of food additives. Dr. Arvidson discussed how the OFAS uses (Q)SAR in their assessments and reviewed the ongoing development of the Chemical Evaluation and Risk Estimation System (CERES) knowledgebase.

Dr. Arvidson explained that (Q)SAR tools are used by his group and by U.S. FDA toxicologists primarily to identify toxicity data gaps and provide specific toxicity testing recommendations during premarket notification consultations.

He noted that FDA staff use multiple (Q)SAR tools and databases, in concert, to maximize the chemical space (i.e., the domain of applicability) of this approach. In addition, they employ a weight-of-evidence, consensus approach to develop predictions and recommendations for the food contact notification review process. Emphasis is placed on fully evaluating and understanding how to run the models before using them. Further, the U.S. FDA takes a conservative approach to interpreting and making decisions based on the output of these models. For example, one positive result among multiple (Q)SAR predictions may trigger a recommendation to evaluate additional structural analogs or conduct additional toxicity testing.

Dr. Arvidson depicted the CERES workflow in the figure.

The CERES system is a food additive knowledgebase developed to improve pre- and post-marketing reviews and promote more robust safety assessments. CERES captures institutional knowledge and consolidates information on chemical structures (including substructures), physical properties, toxicities, mode of



action, metabolism, and exposures, as well as specific regulatory decisions and actions for chemicals of interest. CERES can be used to facilitate the identification of suitable analogs for (Q)SAR analysis and read-across, and to discover useful relationships between new and existing data.

Dr. Arvidson noted that Procter and Gamble (P&G) has donated approximately 40,000 high quality chemical structures to the CERES project. Eventually the U.S. FDA will share CERES with the COSMOS group. The CERES system will be available online when the JRC begins to host the system on their Website.

### Decision Tree for Categorizing Analogs



**Karen Blackburn, Ph.D.**, is a Research Fellow at P&G, Central Product Safety, where she provides technical oversight and collaborates with expert groups to develop risk assessment methods. She outlined a framework for using structural, metabolic, and other properties of chemicals to identify and evaluate the suitability of analogs for use in SAR read-across assessments. The framework was recently published by Dr. Shengde Wu, Dr. Blackburn, and their colleagues at P&G.

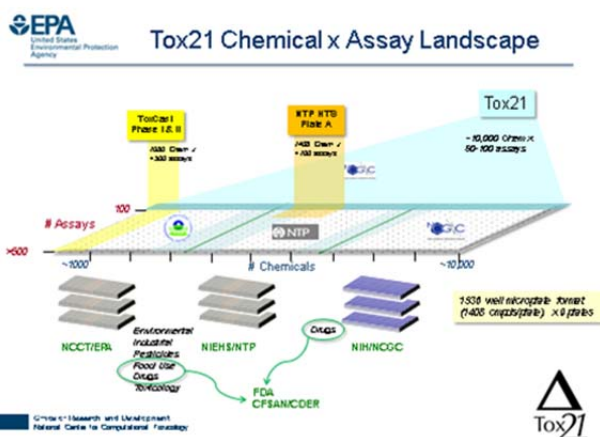
Dr. Blackburn presented a decision tree shown on the left to describe this integral element in their overall approach to SAR assessments.

She explained that the process for characterizing the suitability of candidate analogs involves a chemistry evaluation, a metabolism evaluation, a toxicity review, and a rating of the uncertainty associated with each candidate.

Dr. Blackburn noted that their published case studies demonstrate that the framework can be applied successfully for read-across, and consistently provides reasonable, conservative estimates of no effect levels for substances of interest (SOIs). She stated that her experience developing

and testing the framework suggests that, in some cases, more confidence could be placed in the conservative assessments developed based on high quality analogs identified using the framework than to assessments based on the results of a single animal study on an SOI, given the variability typically associated with such studies.

Dr. Blackburn also presented a PEG-Cocamine case study to illustrate the potential application of the framework for performing read-across to support the safety assessment of a relatively large and complex cosmetic ingredient group. She explained that her group was able to identify analogs that could adequately cover the chemical space represented by all of the ingredients in the group.



**Ann M. Richard, Ph.D.**, is a Research Chemist at the U.S. EPA National Center for Computational Toxicology (NCCT) in the Office of Research and Development (ORD). She leads the NCCT's Distributed Structure-Searchable Toxicology (DSSTox) Database project and manages the cheminformatics components of the ToxCast and Tox 21 programs.

Dr. Richard reviewed the ToxCast and Tox21 projects, presented new cheminformatics approaches used in the Tox21 program, and compared the chemical space of cosmetic ingredients to that of other chemicals in the Tox21 inventory.

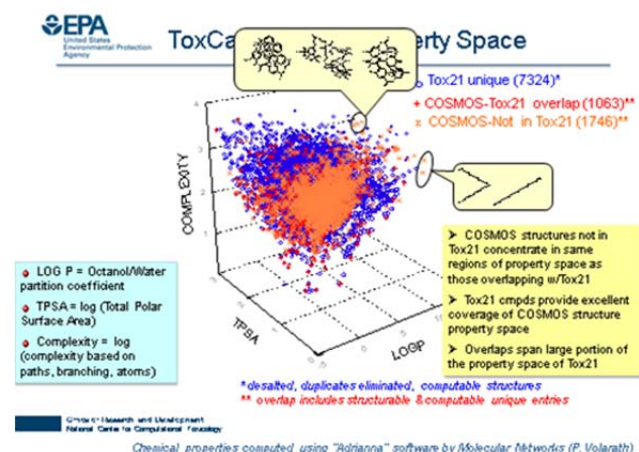
The purpose of ToxCast is to develop the ability to predict in vivo toxicity using computational chemistry and high-throughput screening (HTS) in vitro toxicity tests. The approach involves generating and correlating data in very large datasets from three primary data domains, including chemical structures, in vitro/HTS assay results and in vivo toxicity data. Dr. Richard used the slide on the left to illustrate the Tox21/ToxCast chemical and assay landscapes. The challenge is to

determine how to make best use of all of these mechanistically diverse data to extract meaningful relationships that can be used to predict toxicity.

Mode-of-Action (MoA) (Q)SAR analysis involves identifying chemical signatures or chemotypes from the "intermediate biology" information provided by in vitro testing of chemicals in the broad chemical spaces represented by the Tox21 inventory. Dr. Richard emphasized that developing MoA (Q)SAR approaches is key to enabling the prediction of toxicity of chemicals without having to run all of them through in vitro profiling assays. Developing this capability is critical because of the costs and other practical constraints that preclude testing tens of thousands of chemicals for toxicity.

Dr. Richard explained the importance of her group's analytical chemistry QC efforts to ensure the accuracy of the ToxCast and Tox21 data and enable the discovery of reliable associations among the data domains and reliable predictions based upon these associations.

She used the slide to the right to illustrate the extensive overlap in chemical property space between cosmetic ingredients and the other chemicals in the Tox21 inventory. This overlap shows that ToxCast data and tools offer opportunities to explore the assay space of cosmetic ingredients, search for predictive associations among the relevant data domains, and use the results to enhance read-across and inform safety assessments of these ingredients. NCCT will make all of these data and tools publicly available, online, within the next year. Dr. Richard noted that the NCCT is developing a "dashboard" that will facilitate the use of these data and tools.



The targeted toxicity testing that the Tox21 and ToxCast projects will make possible will substantially reduce the need for whole-animal testing in the future. This is because, for example, these efforts will enable identifying serious data gaps that can be addressed only by having animal tests for a group of chemicals, and testing just one, representative chemical in that group.

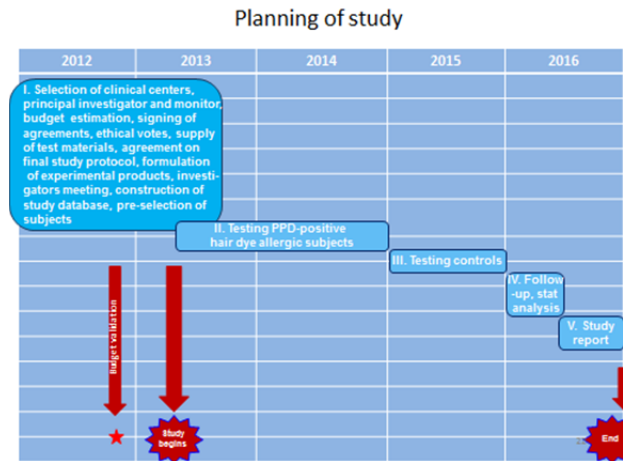
Her presentation is available at <http://www.cir-safety.org/supplementaldoc/tox21-toxcast-programs-using-vitro-hts-data-predict-vivo-outcomes-chemical-perspecti>.

## Nanomaterials in Cosmetics – Kapal Dewan

Ms. Kapal Dewan, Office of Cosmetics and Colors, FDA, explained that the points to consider when assessing the safety of cosmetic products were prepared in context of the absence of premarket approval for cosmetics (with the exception of color additives) and the responsibility that manufacturers bear for the safety of marketed products. Because FDA regulates products, and not technologies, cosmetics manufactured using nanotechnology are subject to the same requirements as other cosmetics. She reviewed the diversity of nanotechnology in cosmetics.

She suggested that, while the existing framework for safety assessment is generally robust and flexible, the special features of nanomaterials warrant special attention to absorption, biodistribution, accumulation, and clearance --- and, as always, considering conditions of use! She encouraged interested parties to offer comments on the draft. The full text of the FDA draft guidance document is available at <http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ucm300886.htm>

## Hair Dye Self-Testing – Carsten Goebel, Ph.D.



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 above. 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 – Ivan Boyer, Ph.D., DABT

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.

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 noted 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.

### Development of Biotransformation Activities: Summary

- **Liver**
  - Many hepatic enzyme systems **mateure rapidly** in newborns
    - Can be very low & variable at ages  $\leq 6$  months
    - Can be comparable or exceed adult capacities by age 6 months to 1 year
  - Some systems mature gradually up to age 1 to 3 years or more
  - Capacities similar to adults’ by age  $\sim 6$  months, with exceptions (depending on the substrate)
- **Skin**
  - Biotransformation generally much **slower in skin than in liver**
  - Development in skin may **parallel** development in liver
    - Neonates & infants  $\leq 6$  months old may have much lower & more variable dermal enzyme activities than older children & adults
    - Children may have dermal enzyme capacities similar to adults’ by age  $\sim 6$  months (depending on the substrate)

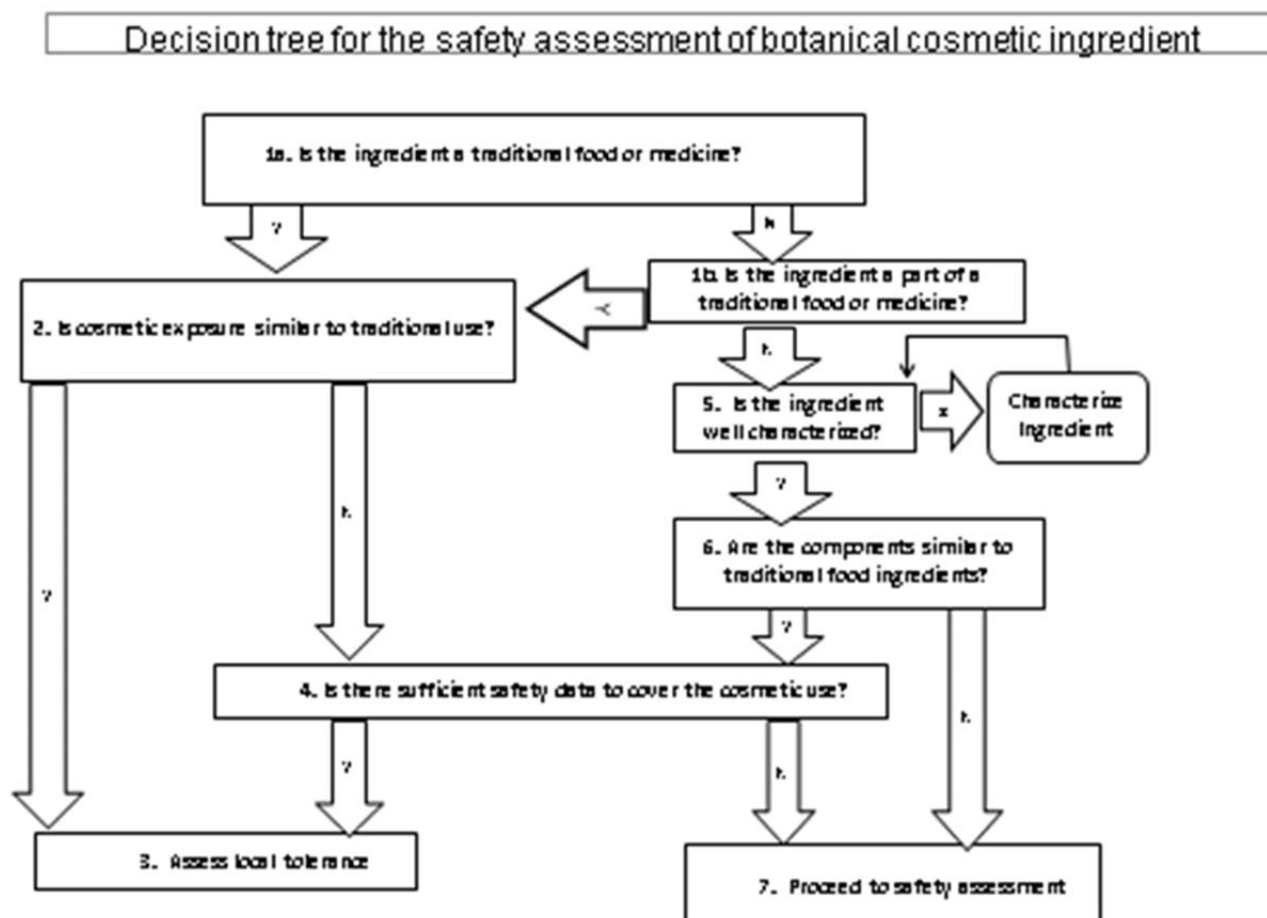
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## Botanical Ingredients Safety Decision Tree – Thomas Re, Ph.D.

The Personal Care Products Council's CIR Science and Support Committee developed a decision tree that finished-product manufacturers could use to assess the safety of botanical cosmetic ingredients. Representing the committee, Dr. Thomas Re, Senior Principle Scientist at L'Oreal S.A., reviewed the decision tree shown in the diagram below, and explained how it would operate. He emphasized that chemical characterization is a key element of the decision tree. Developing a chromatographic 'fingerprint' of specific marker chemicals is encouraged to define the variability of botanicals, to detect adulteration and, thereby, to confirm authenticity. If the decision tree indicates the need for a safety assessment, such an effort may include the following (alone or in combination): thresholds of toxicological concern, read across/chemical grouping, Joint FAO/WHO expert committee on food additives findings, in silico data, structure/activity relationships, metabolic profiling, and in vivo and/or in vitro assays.

The full text of the presentation is available at <http://www.cir-safety.org/supplementaldoc/decision-tree-safety-assessment-botanical-cosmetic-ingredients>.

The Panel indicated that the points addressed in the template were appropriate and mirrored much of the effort of the CIR Expert Panel to capture data about ingredients from botanical sources. They emphasized that future submissions to CIR should address specific chemical compositions and manufacturing details, including especially information specific as to how each of these ingredients is prepared for cosmetic use. The Panel suggested that such information should be available from cosmetic ingredient suppliers, and will likely be provided if finished-product manufacturers insist.



## CIR EXPERT PANEL MEMBERS

### Voting Members

**Wilma F. Bergfeld, M.D.,F.A.C.P.,** Panel Chairman  
Head of Clinical Research and Dermatopathology  
The Cleveland Clinic Foundation

**Donald V. Belsito, M.D., Panel Team Leader**  
Leonard C. Harber Professor of Clinical Dermatology  
Columbia University Medical Center

**Curtis D. Klaassen, Ph.D.**  
Professor of Pharmacology and Toxicology, School of Medicine  
University of Kansas Medical Center

**Paul W. Snyder, D.V.M., Ph.D.**  
Professor of Toxicologic Pathology and Director, Veterinary Clinical Immunology and Histopathology Laboratories,  
School of Veterinary Medicine, Department of Comparative Pathobiology, Purdue University

**Ronald A. Hill, Ph.D.**  
Associate Professor of Medicinal Chemistry  
ULM College of Pharmacy

**James G. Marks, Jr., M.D., Team Leader**  
Professor of Medicine, Chairman of the Division of Dermatology  
Pennsylvania State University College of Medicine  
Milton S. Hershey Medical Center

**Ronald C. Shank, Ph.D.**  
Emeritus Professor, Dept. of Community & Environmental Medicine  
University of California, Irvine

**Thomas J. Slaga, Ph.D.**  
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School of Medicine

**Daniel C. Liebler, Ph.D.**  
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Vanderbilt University School of Medicine

### Non-voting liaison members

**Rachel Weintraub, Esq.**  
Legislative Director & Senior Counsel  
Consumer Federation of America

**Halyna Breslawec, Ph.D.**  
Executive VP – Science  
Personal Care Products Council

**Linda Katz, M.D., M.P.H.**  
Director, Office of Cosmetics and Colors and Chief Medical Officer, CFSAN  
Food and Drug Administration

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Bart Heldreth, PhD - Chemist  
Carla Jackson, Administrative Coordinator  
Wilbur Johnson, MS –Senior Technical Writer  
Julia Linthicum – Data Manager

## **2013 CIR EXPERT PANEL MEETINGS**

Dates:

March 18 – 19, 2013 (Mon-Tues)

June 10 – 11, 2013 (Mon-Tues)

September 9 - 10, 2013 (Mon-Tues)

December 9-10, 2013 (Mon-Tues)

Location: The Madison Hotel  
1177 15th Street, NW  
Washington, DC 20005  
202-862-1600 (Phone)  
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