

Cosmetic Ingredient Review Expert Panel 123rd Meeting (June 11-12) - Findings

June 15, 2012

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Final Safety Assessments

Any interested person who believes that a final safety assessment or final amended safety assessment is incorrect may petition the CIR Expert Panel to amend the safety assessment. Unpublished data cited as references in CIR safety assessments are posted on the CIR website and available for review at the CIR office. Final safety assessments and final amended safety assessments will be posted on the CIR website at www.cir-safety.org.

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, and
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 in reviewing other botanical ingredients, phytosterols and phytosterol esters are not significantly absorbed through the skin and do not result in systemic exposure.

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 (the presence of fluorine appears to enhance the thermal stability), the structure still takes the form 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.

Tentative Safety Assessments

These tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before June 22, 2012. Interested persons are given 60 days to comment, provide information and/or request an oral hearing before the CIR Expert Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, posted on the CIR website, and are available at the CIR office for review by any interested party. **Please submit data and/or comments to CIR by August 22, 2012, or sooner if possible.** These reports may be scheduled for review by the CIR Expert Panel at its **September 10-11, 2012 meeting**.

α -Amino Acids

The CIR Expert Panel issued a tentative safety assessment for public comment with the conclusion that α -amino acids and their salts were safe in the present practices of use and concentration in cosmetics. The 34 ingredients included in this safety assessment are:

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

*Not in current use. Were the ingredients 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 the group.

the CIR Expert Panel noted that Glycine (no stereocenter) and the L-amino acids are GRAS

These ingredients function as hair and skin conditioning agents. The *International Cosmetic Dictionary and Handbook* does not make the distinction as to whether the α -amino acids used in cosmetics are of L- or D-stereochemistry (or are mixtures of L- and D-stereoisomers). The Expert Panel noted that the α -L-amino acids are Generally Recognized As Safe (GRAS) direct food additives by the FDA, as are methionine which is a racemic mixture and glycine which lacks a stereocenter. 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 Voluntary Cosmetic Registration Program (VCRP) has received reported uses of the DL-mixtures in addition to L-amino acids in cosmetics. However, no cosmetic uses were reported for α -amino acids ingredients that are specifically the D-stereoisomers, possibly 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. However, because of the lack of data that specifically support the safety of the D-stereoisomers, the Expert Panel concluded that this safety assessment could not address α -amino acids that are D-stereoisomers only.

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

The CIR Expert Panel issued a tentative report for public comment with the conclusion that bis-diglyceryl polyacyladipate-1 and bis-diglyceryl polyacyladipate-2 are safe in the present practices of use and concentration in cosmetics.

These ingredients are mixed fatty acid esters used as emollients in cosmetics. Method of manufacturing and impurities data were received, eliminating earlier data gaps. A multitude of structural configurations are possible within each bis-diglyceryl polyacyladipate ingredient, but they are uniformly large compounds that are highly

lipid soluble and not very water soluble. Data gaps remain regarding toxicokinetics and carcinogenicity data. However, bis-diglyceryl polyacyladipate-2 and bis-diglyceryl polyacyladipate-1 molecular size and solubility are such that they are not expected to pass through the stratum corneum of the skin, so significant systemic exposure is not expected.

Borosilicate Glasses

The CIR Expert Panel issued a tentative report for public comment with the conclusion that borosilicate glasses are safe in the present practices of use and concentration in cosmetic products. The 5 ingredients included in this safety assessment are:

calcium sodium borosilicate	silver borosilicate*
calcium aluminum borosilicate	zinc borosilicate*
calcium titanium borosilicate	

*Not 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. While there is a notable lack of data on toxicokinetics and repeated dose toxicity, these ingredients are large, stable molecules that are not soluble, would not penetrate the skin, and could not be associated with systemic toxicity. They are not dermal irritants or sensitizers.

Chlorphenesin

The CIR Expert Panel issued a tentative report for public comment with the conclusion that Chlorphenesin is safe for use in cosmetics in the present practices of use and concentration.

This ingredient is a widely used cosmetic biocide. The Expert Panel acknowledged the potential immunosuppressive activity of chlorphenesin, based on in vitro assay results. However, after considering that in vivo dosing with chlorphenesin did not increase the susceptibility of animals to infections or act as a tumor promoter in in vivo studies, it was agreed that there was very little or no manifestation of immunosuppressive activity.

Some confusion is apparent in that a drug, chlorphenesin carbamate (CAS No. 886-74-8) is also referred to as "chlorphenesin." The drug chlorphenesin carbamate is a muscle relaxant that can depress the CNS. The Panel concluded that the cosmetic ingredient, chlorphenesin (CAS No. 104-29-0), does not have similar activity, based on the use concentration, the dermal route of exposure, and the resulting low serum concentrations.

Dialkyl Malates

The CIR Expert Panel issued a tentative report for public comment with the conclusion that dialkyl malates are safe in the current practices of use and concentration.

The 6 ingredients included in this safety assessment are:

dibutylsebacate*	diisooamyl malate*
di-C12-13 alkyl malate	diisostearyl malate
diethylhexyl malate	dioctylododecyl malate*

*Not in current use. Were the ingredients 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 the group.

These ingredients have general functionality in cosmetics as skin conditioning agents. Genotoxicity data in a mammalian assay system and data from a 28-day dermal toxicity study were received, eliminating earlier data gaps. Absent data that could address the dermal sensitization potential of dioctylododecyl malate were not received, the Panel reconsidered the available case literature for octylododecanol on which the data request had been based. The Panel determined that this information was not an adequate basis on which to suggest that dioctylododecyl malate would be a sensitizer in cosmetic formulations. Supporting this view were the data for other dialkyl malates that demonstrated an absence of dermal sensitization in animal and human studies.

Dimethicone Crosspolymers

The CIR Expert Panel issued a tentative report for public comment with the conclusion that dimethicone crosspolymers are safe in the current practices of use and concentration.

The 62 ingredients included in this safety assessment are:

acrylates/bis-hydroxypropyl dimethicone crosspolymer*	dimethicone/PEG-10/15 crosspolymer
behenyl dimethicone/bis-vinyldimethicone crosspolymer	dimethicone/PEG-15 crosspolymer*
bis-phenylisopropyl phenylisopropyl dimethicone/vinyl dimethicone crosspolymer*	dimethicone/phenyl vinyl dimethicone crosspolymer
bis-vinyldimethicone/bis-isobutyl PPG-20 crosspolymer*	dimethicone/polyglycerin-3 crosspolymer
bis-vinyldimethicone crosspolymer*	dimethicone/PPG-20 crosspolymer
bis-vinyldimethicone/ PEG-10 dimethicone crosspolymer*	dimethicone/titanate crosspolymer*
bis-vinyldimethicone/PPG-20 crosspolymer*	dimethicone/vinyl dimethicone crosspolymer
butyldimethicone methacrylate/methyl methacrylate crosspolymer*	dimethicone/vinyltrimethylsiloxysilicate crosspolymer
C30-45 alkyl cetearyl dimethicone crosspolymer	diphenyl dimethicone crosspolymer*
C4-24 alkyl dimethicone/ divinyl dimethicone crosspolymer	diphenyl dimethicone/vinyl diphenyl dimethicone/silsesquioxane crosspolymer
C30-45 alkyl dimethicone/ polycyclohexane oxide crosspolymer	divinyldimethicone/dimethicone crosspolymer
cetearyl dimethicone crosspolymer	hydroxypropyl dimethicone/polysorbate 20 crosspolymer*
cetearyl dimethicone/vinyl dimethicone crosspolymer	isopropyl titanium triisostearate/triethoxysilylethyl polydimethylsiloxylethyl dimethicone crosspolymer
cetyl dimethicone/bis-vinyldimethicone crosspolymer	lauryl dimethicone PEG-15 crosspolymer*
cetyl hexacosyl dimethicone/bis-vinyldimethicone crosspolymer*	lauryl dimethicone/polyglycerin-3 crosspolymer*
crotonic acid/vinyl C8-12 isoalkyl esters/VA/bis-vinyldimethicone crosspolymer*	lauryl polydimethylsiloxylethyl dimethicone/bis-vinyldimethicone crosspolymer*
dimethicone/bis-isobutyl PPG-20 crosspolymer	PEG-10 dimethicone crosspolymer
dimethicone/bis-vinyldimethicone/silsesquioxane crosspolymer*	PEG-12 dimethicone crosspolymer
dimethicone crosspolymer	PEG-8 dimethicone/polysorbate 20 crosspolymer*
dimethicone crosspolymer-3	PEG-12 dimethicone/bis-isobutyl PPG-20 crosspolymer*
dimethicone/divinyldimethicone/silsesquioxane crosspolymer	PEG-12 dimethicone/PPG-20 crosspolymer*
dimethicone/lauryl dimethicone/bis-vinyldimethicone crosspolymer*	PEG-10 dimethicone/vinyl dimethicone crosspolymer
dimethicone/PEG-10 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*
trimethylsiloxy silicate/ dimethicone crosspolymer*
vinyl dimethicone/lauryl/behenyl dimethicone crosspolymer*
vinyl dimethicone/lauryl dimethicone crosspolymer
vinyl dimethicone/methicone silsesquioxane crosspolymer
vinyl dimethyl/trimethylsiloxy silicate/dimethicone crosspolymer*
vinyl dimethyl/trimethylsiloxy silicate stearyl dimethicone crosspolymer*

*Not in current use. Were the dimethicone crosspolymers 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 the group.

These large, stable, insoluble molecules are used in cosmetics for functions such as bulking and non-aqueous viscosity-increasing agents. These cosmetic ingredients will not penetrate the skin and cannot cause systemic toxicity. They are neither toxicants in acute toxicity studies, nor dermal irritants or sensitizers.

A lack of data on possible residual monomer content was noted. Data on the concentrations of residual monomers in the dimethicone crosspolymers would assist the Panel's review. The residual monomers at issue are:

α -methylstyrene
bis-vinyldimethicone
methyl methacrylate
butyldimethylsilylmethacrylate
vinyl cyclohexene oxide
vinyl acetate
 α,ω -divinyl alkenes (C4-20)
bis-vinyl phenylmethyl dimethicone
allyl alcohol

isobutanol
titanium species used in crosslinking [(0-IPr)₄ or (0-iPr)₂Cl₂]
unidentifiable diamine crosslinking agent in silicone quaternium-16/glycidoxy dimethicone crosspolymer
styrene
divinyl benzene
allyl polyglyceryl-3
bisvinyl trifluoropropyl methicone (if n \leq 8)

Microbial Polysaccharide Gums

The CIR Expert Panel issued a tentative report for public comment with the conclusion that microbial polysaccharide gums are safe in the present practices of use and concentration in cosmetics.

The 34 ingredients included in this safety assessment are:

xanthan gum;
hydroxypropyl xanthan gum;*
undecylenoyl xanthan gum;*
dehydroxanthan gum;
xanthan gum crosspolymer;
xanthan hydroxypropyltrimonium chloride;*
gellan gum;
welan gum;*
biosaccharide gum-1;
biosaccharide gum-2;
biosaccharide gum-3;*
biosaccharide gum-4;
biosaccharide gum-5;*
pseudoalteromonas exopolysaccharides;*
dextran;
carboxymethyl dextran;*
dextran hydroxypropyltrimonium chloride;*

sodium carboxymethyl dextran;
dextran sulfate;
sodium dextran sulfate;
sclerotium gum;
hydrolyzed sclerotium gum;
beta-glucan;
beta-glucan hydroxypropyltrimonium chloride;*
beta-glucan palmitate;*
hydrolyzed beta-glucan;*
oxidized beta-glucan;*
sodium carboxymethyl beta-glucan;
pullulan;
myristoyl pullulan;*
levan;*
rhizobian gum;
hydrolyzed rhizobian gum; and
alcaligenes polysaccharides.

*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 the group.

The Panel noted that the biological activity of lipopolysaccharides is unlike that of the polysaccharide gums covered in this report. To avoid confusion, the Panel changed the name of this report from microbial polysaccharides to microbial polysaccharide gums.

The polysaccharide gums addressed in this safety assessment are used for a wide variety of functions in cosmetics, ranging from emulsion stabilization to skin conditioning. Although these ingredients are produced primarily by microorganisms, the cosmetic ingredients are purified during manufacture and microbial contamination is not a concern. These very large molecules are not expected to penetrate the stratum corneum. The Panel initially expressed concern for a study that reported that 5% aq. xanthan gum caused irritation in rabbits. However, this was a very old study on shaved skin with no details provided; leading the Panel to surmise that the irritation was an artifact of the methodology and not caused by the xanthan gum. There was no evidence of microbial polysaccharide gums producing sensitization in any of the other human and non-human testing. The Panel also remarked on the induction of colon carcinogenesis with oral exposure to sodium dextran sulfate. Sodium dextran sulfate is commonly used for induction of colitis in a well-characterized mouse model, but the mode of action of sodium dextran sulfate induced colitis in the mouse is not relevant to human exposure.

Panax Ginseng Root and Related Ingredients

The CIR Expert Panel issued a tentative report for public comment with the conclusion that *Panax ginseng* root and related ingredients are safe in the present practices of use and concentration in cosmetics.

The 13 ingredients included in this safety assessment are:

hydrolyzed ginseng root*
hydrolyzed ginseng root extract
hydrolyzed ginseng saponins*
panax ginseng root

panax ginseng root extract*
panax ginseng root oil*
panax ginseng root powder
panax ginseng root protoplast*

panax ginseng root water*
panax japonicus root extract*
panax notoginseng root
panax notoginseng root powder*

panax quinquefolium root extract

*Not in current use. Were the ginseng root-derived ingredients 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 the group.

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 experience, 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.

There is a report of pulegone in *Panax quinquefolium* root oil, which is not a cosmetic ingredient. Pulegone toxicity is a concern, and because the extract of the root may be prepared using a variety of solvents, the Panel was concerned that 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 such that toxicity would be seen with cosmetic use.

Polyether Lanolins

The CIR Expert Panel issued a tentative report for public comment with the conclusion that polyether lanolins are safe in the present practices of use and concentration in cosmetics.

The 39 ingredients included in this safety assessment are:

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

*Not in current use. Were the polyether lanolins 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 the group.

PPG-5 lanolin wax and PPG-5 lanolin wax glyceride are part of a larger group of cosmetic ingredients, the polyether lanolins.

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.

Vitis Vinifera (Grape)-Derived Ingredients

The CIR Expert Panel issued a tentative report for public comment with the conclusion that *Vitis vinifera* (grape)-derived ingredients are safe in the present practices of use and concentration in cosmetics.

The 24 ingredients included in this safety assessment are:

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 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 the group.

The Panel added hydrolyzed grape fruit and hydrolyzed grape skin to this safety assessment. These 2 ingredients are obtained from crude materials that are hydrolyzed and not specifically protein hydrolysates. The Panel considered that the existing data apply to the safety of these ingredients.

While grape and grape juice did produce an increase in mutations in certain bacterial studies, the Panel noted that such findings are a part of a history of positive Ames tests with food products. Despite some evidence of genotoxicity in bacterial assays, constituents of foods such as grapes, e.g. flavonoids, do not appear to be genotoxic in mammalian species in vivo. Additionally, *Vitis vinifera*-derived extracts can inhibit tumor promotion.

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 (e.g., isoflavones). Although no dermal absorption data were available, in the Panel's experience, phytosterols and phytosterol esters are not significantly absorbed and do not result in systemic exposure, and extensive data show that these constituents are not estrogenic, are not reproductive toxicants, are not genotoxic, and are not carcinogenic.

Insufficient Data Announcements

For insufficient data announcements, interested persons are given an opportunity to comment, provide information and/or request an oral hearing before the CIR Expert Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, 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 August 15, 2012, or sooner if possible. These ingredient reports may be scheduled for review by the CIR Expert Panel at its September 10-11, 2012 meeting.

Fatty Acid Amidopropyl Dimethylamines

The CIR Expert Panel requested additional data to support the safety of fatty acid amidopropyl dimethylamines.

The additional data needed are: (1) percutaneous absorption of the ingredient that has the shortest chain fatty acids (e.g., lauramidopropyl dimethylamine), and if it is absorbed; (2) reproduction and developmental toxicity data; and (3) sensitization and irritation data on oleamidopropyl dimethylamine at use concentration.

The fatty acid amidopropyl dimethylamines in this safety assessment are:

almondamidopropyl dimethylamine	lauramidopropyl dimethylamine	ricinoleamidopropyl dimethylamine
avocamidopropyl dimethylamine	linoleamidopropyl dimethylamine	sesamidopropyl dimethylamine
babassuamidopropyl dimethylamine	minkamidopropyl dimethylamine	soyamidopropyl dimethylamine
behenamidopropyl dimethylamine	myristamidopropyl dimethylamine	stearamidopropyl dimethylamine
brassicamidopropyl dimethylamine	oatamidopropyl dimethylamine	sunflowerseedamidopropyl dimethylamine
cocamidopropyl dimethylamine	oleamidopropyl dimethylamine	tallamidopropyl dimethylamine
dilinoamidopropyl dimethylamine	olivamidopropyl dimethylamine	tallowamidopropyl dimethylamine
isostearamidopropyl dimethylamine	palmitamidopropyl dimethylamine	wheat germamidopropyl dimethylamine

While this was the first time the Panel has reviewed these ingredients, each of them is a variation of the amidoamine impurities discussed at length as potential sensitizers in the previous fatty acid amidopropyl betaines safety assessment. In the conclusion of the fatty acid amidopropyl betaines safety assessment, the Expert Panel concluded that ingredients with such impurities were safe in cosmetic ingredients as long as they were formulated to be non-sensitizing, which may be determined based on a quantitative risk assessment.

Nylon Polymers

The CIR Expert Panel requested additional data to support the safety of nylon polymers.

The additional data needed include: (1) irritation and sensitization of nylon-12 at use concentration; (2) other relevant toxicological (repeated dose, genotoxicity, carcinogenicity, etc.) data on nylon-12; and (3) genotoxicity data on the precursor, dodecanolactam.

The nylon polymers in this safety assessment are:

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

This was the Expert Panel's first review of this ingredient group. The Expert Panel noted that the size of the polymers would appear to preclude significant dermal penetration, but expressed concern that data were not available. Because of the large number of uses of nylon-12, the Expert Panel was hopeful that safety test data would be available and noted that this safety assessment would be greatly improved if such toxicity data were provided. The Panel also discussed the possible need for other data for assessing the safety of individual precursors, including adipic acid, hexylenediamine, caprolactam, dedecanolactam, decylenediamine, decanedioic acid, 11-aminoundecanoic acid, and 12-aminododecanoic acid. If the additional data requested for nylon polymers demonstrates an absence of toxicity, the Panel reasoned that such data could support the safety of residual precursors that might be present in nylon polymers used as cosmetic ingredients.

Re-Reviews

Formic Acid – reopened

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.

New Data

Achillea Millefolium Extract – reopened

The Panel reopened this safety assessment to incorporate the large amount of new data provided, and to consider that these data may support the safety of this ingredient as used in cosmetics.

Previously, the CIR published a safety assessment for achillea millefolium extract with the conclusion that the available data were insufficient to support the safety as used in cosmetics (the common name for this plant is yarrow). The new data address the data needs and suggest that this ingredient may be safe for use in cosmetics. The Panel also determined to add the following *Achillea millefolium*-derived ingredients:

achillea millefolium flower extract	achillea millefolium flower water
achillea millefolium flower/leaf/stem extract	achillea millefolium oil

Interested parties should use this opportunity to provide additional data for each ingredient, including the concentration of use.

Hypericum Perforatum Extract and Oil - reopened

The Panel reopened this safety assessment to incorporate the large amount of new data provided and to consider that these data may support the safety of these ingredients as used in cosmetics.

Previously, the CIR published a safety assessment for hypericum perforatum extract and oil with the conclusion that the available data were insufficient to support the safety as used in cosmetics (the common name for this plant is St. John's wort). The new data address the data needs and suggest that this ingredient may be safe for use in cosmetics. The Panel also determined to add the following *Hypericum perforatum*-derived ingredients:

hypericum perforatum callus culture extract	hypericum perforatum flower/leaf/stem extract
hypericum perforatum flower extract	hypericum perforatum flower/twig extract
hypericum perforatum flower/leaf extract	hypericum perforatum leaf extract

Interested parties should use this opportunity to provide additional data for each ingredient, including the concentration of use.

123rd Meeting Notes

CIR Expert Panel Member Recognition



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.

Director's Report

Dr. Andersen acknowledged the large number of ingredient reports on the agenda for Panel review at this meeting. He explained that adjustments had been made for the March 2012 meeting to accommodate the SAR workshop. Reports that were postponed now are coming back onto the agenda. As a consequence, meetings for the rest of the year likely will be busy. Dr. Andersen also remarked that:

- work is on track to submit final safety assessments to the *International Journal of Toxicology* for peer review and publication
- a recently published review article addressing self-testing for contact sensitization to hair dyes (*Contact Dermatitis* 66:300-311, 2012) will be considered when the Panel next addresses a hair dye ingredient
- the summary of the March SAR workshop presented by Dr. Boyer will be included in the minutes of this meeting

Dr. Andersen noted that FDA has agreed to provide a briefing for the Panel regarding its recently issued draft guidance document. The FDA liaison for this meeting, Dr. Stan Milstein, encouraged all interested parties to comment on the draft guidance and introduced Kapal Dewan to make the presentation.

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 explained 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>.

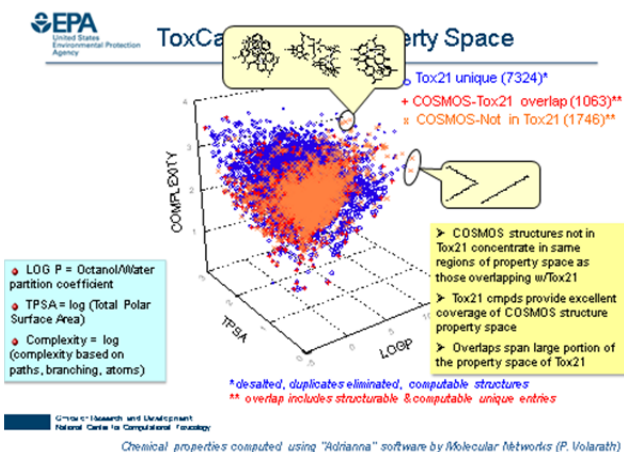
SAR workshop summary – Dr. Ivan Boyer

CIR's senior toxicologist, Ivan Boyer, Ph.D., DABT, briefly summarized the presentations made at the CIR Expert Panel SAR workshop in March 2012. He highlighted the fundamental paradigm shift away from *in vivo* animal studies to a range of alternative approaches that include *in vitro* assays, *in vivo* studies not using mammalian test species, and computational toxicology in which the mode of action is a critical parameter. That European cosmetics legislation, among other factors, is driving the need to move in this direction is unquestioned, but only a few endpoints may be attainable through the new approaches in the short term, including dermal penetration, skin irritation/sensitization, and genotoxicity. The work that is underway at FDA, EPA and other government agencies and in industry is being conducted in a remarkably open manner with data sharing. Proctor & Gamble and L'Oréal are among the industry partners of these agencies to facilitate the development of alternative toxicity-testing strategies and methods that meet the goals of the new paradigm.

The full text of Dr. Boyer's re-cap is available at <http://www.cir-safety.org/supplementaldoc/recap-march-2012-workshop-introduction-sar-speaker>.

Computational Toxicology Briefing – Dr. Ann Richard

Following the SAR Workshop during the March 2012 meeting, the CIR Expert Panel asked for periodic updates on advances in Computational Toxicology. In particular, they asked to be briefed on defining the chemical property spaces of chemicals of interest in a systematic manner. This issue is critical for determining the amenability of new computational methods and data to cosmetic ingredient safety assessments.



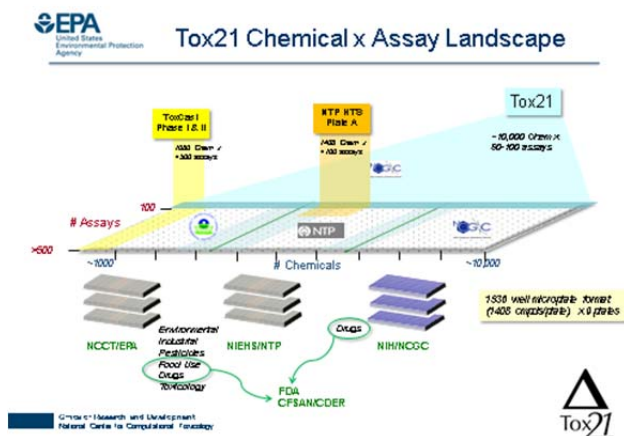
Mode-of-Action (MoA) (Q)SAR analysis involves identifying chemical signatures or chemotypes from the “intermediate biology” information provided by *in vitro* testing of chemicals in the broad chemical spaces represented by the Tox21 inventory. Dr. Richard emphasized that developing MoA (Q)SAR approaches 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 on the left 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 publically 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>.



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.

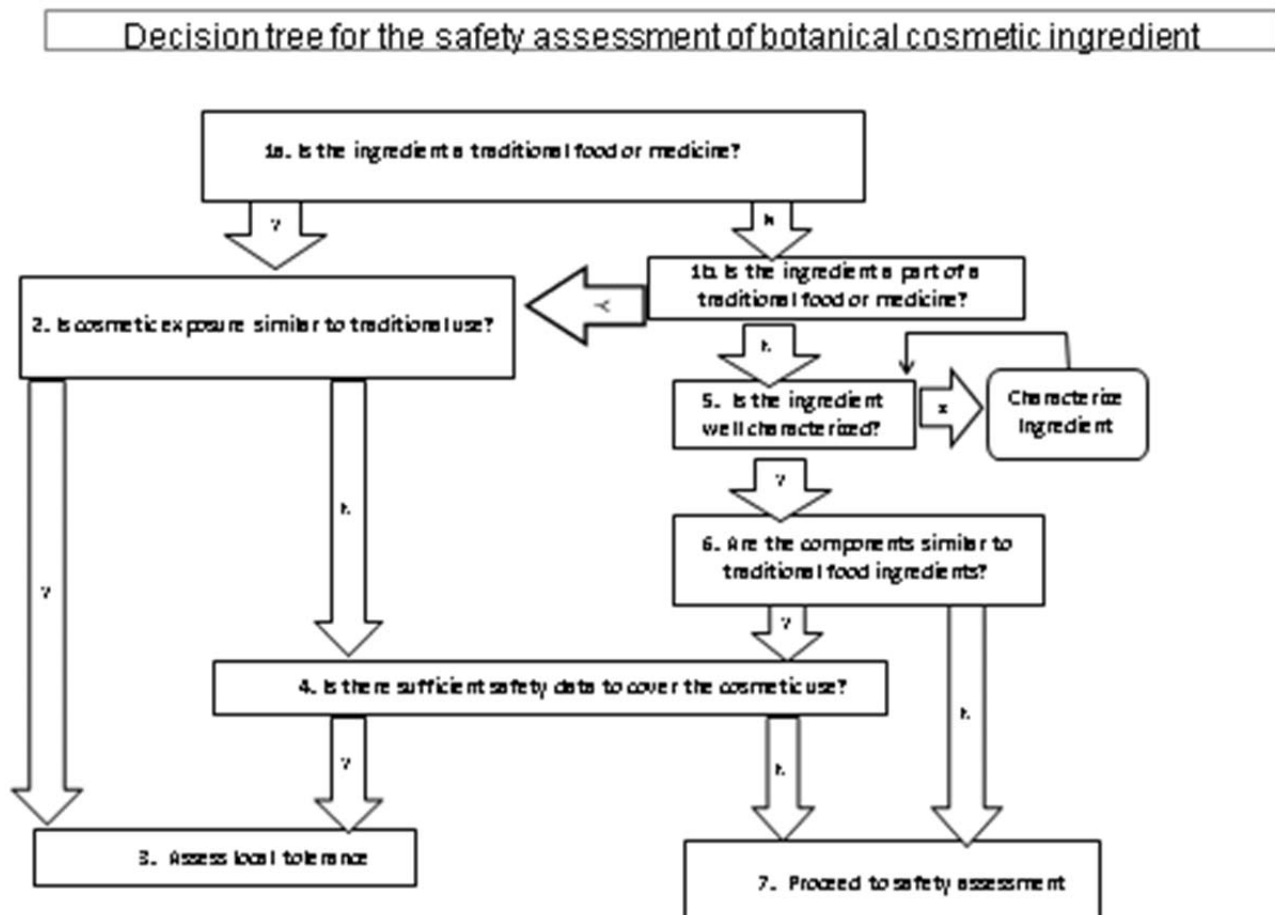
The purpose of ToxCast is to develop the ability to predict *in vivo* toxicity using computational chemistry and high-throughput screening (HTS) *in vitro* toxicity tests. The approach involves generating and correlating data in very large datasets from three primary data domains, including chemical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

Botanical Ingredients Safety Decision Tree – Dr. Thomas Re

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.



Report tabled

The safety assessment on tin oxide was tabled, pending clarification of the form of tin oxide (stannic [tin(IV) oxide] or stannous [tin(II) oxide]) tested in some of the studies and subsequent deletion of study summaries on metallic tin, tin(II) oxide, and tin(II) chloride.

The CIR Expert Panel noted that tin(IV) oxide is being used in cosmetics, but that metallic tin is not being used. The Panel determined that metallic tin should be deleted from the safety assessment.

The Panel also determined that the available data on tin(II) oxide or tin(II) chloride cannot be used to evaluate the safety of tin(IV) oxide. To make this more clear, it was determined that tin(IV) oxide should replace the INCI name (tin oxide) for this ingredient in the report title, ensuring that the name of the ingredient used in cosmetics is consistent with its chemical structure.

The Expert Panel acknowledged that pneumoconiosis can result from high levels of human inhalation exposure to tin oxide dust, but, also, that this level of exposure to tin oxide would not be associated with the use of cosmetic products. Another concern that was raised by the Panel relates to the current use of tin(IV) oxide at

concentrations up to 5% in eye area cosmetics, in the absence of safety test data at this concentration. Therefore, the Panel is requesting that industry provide any available skin irritation data on 5% tin(IV) oxide.

2013 Review Priorities

The Draft 2013 Priority list has been prepared. The list was based on use data from FDA's Voluntary Cosmetic Registration Program (VCRP), received from FDA in May, 2012.

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 included in a group of 160 alkyl PEG/PPG ethers. Another possibility would be to take citrus medica limonum (lemon) fruit extract and create a large group of citrus ingredients. We expect the Personal Care Products Council to nominate a specific hair dye ingredient.

The CIR Expert Panel will be provided with potential groupings before a final priority decision is made. CIR anticipates receiving comments from the industry and public, especially regarding creating an appropriate group for each listed ingredient. The Panel will again review this list and any public comments at the September, 2012 meeting at which time a Final 2013 Priority List will need to be issued.

Ingredients on the 2013 Draft Annual Priority List are:

pentaerythrityl tetra-di-t-butyl hydroxyhydrocinamate	- 475 uses	pyrus malus (apple) fruit extract	- 398 uses
hydrogenated polydecene	- 455 uses	magnesium sulfate	- 393 uses
sodium benzotriazolyl butylphenol sulfonate	- 454 uses	avena sativa (oat) kernel extract	- 377 uses
maltodextrin	- 442 uses	ceramide 3	- 377 uses
trehalose	- 440 uses	potassium cetyl phosphate	- 361 uses
tocotrienols	- 436 uses	butyrospermum parkii (shea) butter extract	- 361 uses
citrus medica limonum (lemon) fruit extract	- 421 uses	glucose	- 350 uses
centella asiatica extract	- 418 uses	helianthus annuus (sunflower) seed extract	- 341 uses
PPG-5-ceteth-20	- 414 uses	hydrogen peroxide	- 335 uses
phytosterols	- 408 uses	hair dye ingredient	- to be determined

CIR will also re-review safety assessments originally performed in 1998. These will include:

alpha hydroxyl acids (e.g., glycolic and lactic acids)	polyvinylpyrrolidone (PVP)
dioctyl sodium sulfosuccinate	iodopropynyl butylcarbamate (IPBC)
HC yellow no. 4	sodium alpha-olefin sulfonates
HC orange no. 11	polyvinyl alcohol

Scientific Literature Reviews

- **These three reviews are currently posted on the CIR website at <http://www.cir-safety.org/ingredients/glossary/all>**
 - hydrolyzed protein
 - methyl glucose polyethers and esters
 - source amino acids
- **These literature reviews are under development and may be posted before the next meeting.**
 - amino acid alkyl amides
 - chamomille-derived ingredients
 - modified terephthalate polymers
 - nitrocellulose
 - palmitoyl oligopeptides
 - talc
 - tromethamine

Next CIR Expert Panel Meeting - Monday and Tuesday, September 10-11, 2012 at the Madison Hotel, 1177 Fifteenth Street, NW, Washington, DC 20005 --- Please contact Carla Jackson (jacksonc@cir-safety.org) at CIR before the meeting if you plan to attend.

►►IMPORTANT CHANGE◀◀

CIR no longer includes an order form listing CIR safety assessments available for sale. Because all CIR documents will be posted on the web site, they will be freely available for comment (scientific literature reviews and tentative reports) or for downloading and retention (final reports).