Announcement

Cosmetic Ingredient Review Expert Panel
121st Meeting (December 12-13, 2011) - Findings

December 16, 2011

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    - Tin oxide
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  - **Next CIR Expert Panel Meeting – Monday and Tuesday, March 5-6, 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/further 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 Unpublished data cited as references in CIR safety assessments are posted on the CIR website and available for review at the CIR office.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.

Alkyl Glyceryl Ethers

Ethylhexylglycerin and the other 10 alkyl glyceryl ethers listed below are safe in the present practices of use and concentration.

These ingredients are characterized by alkyl chains terminated on one end by glycerin via an ether linkage. The ingredients function mostly as surfactants or skin conditioning agents in cosmetics. The CIR Expert Panel noted that cetyl glyceryl ether and chimyl alcohol both are listed as cosmetic ingredients in the *International Cosmetic Ingredient Dictionary and Handbook* but appear to be identical. Because both are listed, both are included in the list of alkyl glyceryl ethers.

While toxicokinetics, single-dose and repeat-dose toxicity data, reproductive and developmental toxicity data, genotoxicity data, and dermal irritation and sensitization data were available for only ethylhexylglycerin, the Panel considered that these data could be extended to support the safety of this entire group. All ingredients are alkyl glyceryl ethers, with similar physicochemical properties, functions and concentrations in cosmetics.

Batyl Alcohol
Caprylyl Glyceryl Ether*
Cetyl Glyceryl Ether/Chimyl Alcohol
Ethylhexylglycerin
Glyceryl Allyl Ether*
Glyceryl Capryl Ether*
Glyceryl Lauryl Ether
Isodecyl Glyceryl Ether*
Isostearyl Glyceryl Ether
Oleyl Glyceryl Ether*

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.

2-Amino-4-Hydroxyethylaminoanisole and 2-Amino-4-Hydoxyethylaminoanisole Sulfate

2-amino-4-hydroxyethylaminoanisole and its sulfate salt are safe as oxidative hair dyes, but should not be used in hair dye products in which N-nitroso compounds may be formed.

Currently the free base is not used – only the sulfate salt is reported to be used. Were the free base to be used in the future, the expectation is that it would be used at concentrations similar to the use concentrations for the sulfate salt.

While nitrosamine content of these hair dyes has not been reported, these are secondary amines and potentially can be nitrosated. Accordingly, their use should be restricted to hair dye formulations to avoid formation of N-nitroso compounds.

The CIR Expert Panel noted that the use of oxidative hair dye formulations involves exposure to precursors and coupling agents as well as to their reaction products. Specifically, 2-amino-4-hydroxyethylaminoanisole sulfate is a coupler reacted with a precursor in the presence of an oxidizing agent to produce the final dye product. While reaction intermediates may be formed, human exposure is to the precursors and coupling agents and to reaction products, not the reaction intermediates. The exposures to the precursors and couplers are low (they are consumed in the color forming reaction), and the exposures to reaction products are even lower (they are adsorbed into the hair shaft itself and physically retained there). Therefore, safety assessments of oxidative hair dyes are driven by the toxicological evaluation of the ingredients (i.e. precursors and coupling agents), more than by the reaction products formed during use, and not at all by reaction intermediates. In this safety assessment, single-dose and repeated-dose toxicity data, reproductive and developmental toxicity, genotoxicity, dermal irritation and sensitization, and hair dye epidemiology data were available for the sulfate salt.

Decyl Glucoside and Other Alkyl Glucosides

Decyl glucoside and the 18 additional alkyl glucosides listed below are safe in the present practices of use and concentration when formulated to be non-irritating.

While toxicokinetics, single-dose and repeat-dose toxicity data, reproductive and developmental toxicity data, genotoxicity data, and dermal irritation and sensitization data were available for only a few of these alkyl glucosides, the CIR Expert Panel considered that the extensive data from previous CIR assessments on fatty alcohols could be used in reaching the conclusion for this entire group. The Panel also noted that alkyl glucosides may enhance the dermal penetration of other ingredients and that care should be taken in when formulating with other ingredients whose for which safety was predicated on their expected low dermal penetration.

Decyl Glucoside
Arachidyl Glucoside
Butyl Glucoside*
C10-16 Alkyl Glucoside*
C12-18 Alkyl Glucoside*
C12-20 Alkyl Glucoside
C20-22 Alkyl Glucoside*
Caprylyl/Capryl Glucoside
Caprylyl Glucoside
Cetearyl Glucoside
Coco-Glucoside
Ethyl Glucoside
Hexadecyl D-Glucoside
Isostearyl Glucoside*
Lauryl Glucoside
Myristyl Glucoside
Octadecyl D-Glucoside
Octyldodecyl Glucoside*
Undecyl Glucoside*

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.

Pentaerythrityl tetraesters

The 16 penaerythrityl tetraesters listed below were found safe in the present practices of use in cosmetic ingredients.

The CIR Expert Panel noted that toxicokinetics, single-dose and repeat-dose toxicity data, reproductive and developmental toxicity data, genotoxicity data, and dermal irritation and sensitization data were not available for every ingredient. The Panel reasoned that data on any ingredient could be used to support the safety of others in the group because the structures of these ingredients includes an identical core pentaerythrityl moiety, the tetraesters vary principally by chain length, and the ingredients are used in similar ways in cosmetic products.

The Panel received additional data clarifying that products containing high concentrations of pentaerythrityl tetraisostearate and pentaerythrityl tetraethylhexanoate are not spray products. While these ingredients may be used in cosmetic sprays and aerosols, the predominantly non-respirable particle size produced from the use of such products, together with the small actual exposure in the breathing zone and the concentrations at which these ingredients are being used, suggests that inhalation would not be a significant route of exposure that might lead respiratory or systemic toxic effects.

Pentaerythrityl Tetraisostearate
Pentaerythrityl Tetra C5-9 Acid Esters*
Pentaerythrityl Tetra C5-10 Acid Esters*
Pentaerythrityl Tetracaprylate/ Tetracaprate
Pentaerythrityl Tetralaurate
Pentaerythrityl Tetramyristate*
Pentaerythrityl Tetrastearate
Pentaerythrityl Tetrabehenate
Pentaerythrityl Tetracocoate*
Pentaerythrityl Tetraoleate*
Pentaerythrityl Tetraethylhexanoate
Pentaerythrityl Tetraethylhexanoate/ Benzoate
Pentaerythrityl Tetrabehenate/ Benzoate/ Ethylhexanoate
Pentaerythrityl Tetrabenzoate*
Pentaerythrityl Tetraisononanoate
Pentaerythrityl Tetrapelargonate

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.

Sodium Lauriminodipropionate, Lauriminodipropionic Acid, And Disodium Lauriminodipropionate

Sodium lauriminodipropionate, lauriminodipropionic acid, and disodium lauriminodipropionate are safe as cosmetic ingredients in the present practices of use and concentration.

The CIR Expert Panel issued this final amended safety assessment based on new data regarding single-dose and repeated-dose toxicity, reproductive and developmental toxicity, genotoxicity, and dermal irritation and sensitization on sodium lauriminodipropionate. The acid and the disodium salt are similar in structure to the monosodium salt and have similar functions in cosmetics, but are not in current use. As they currently have no reported uses, were the acid and the disodium salt to be used in the future, the expectation is that they would be used at concentrations similar to the monosodium salt.

The Panel noted that the available data remain insufficient to support the safety of the related ingredient, sodium lauraminopropionate.

Tentative Safety Assessments and Tentative Amended Safety Assessments

For tentative safety assessments, 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 22, 2012, or sooner if possible.*** *These ingredient reports may be scheduled for review by the CIR Expert Panel at its* ***March 5-6, 2011 meeting****. Tentative safety assessments will be posted on the CIR website at www.cir-safety.org.*

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.

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. 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 expressed concern over the specifications of two disodium laureth sulfosuccinate trade name mixtures, which indicated that these products were positive for formaldehyde/formalin. The Panel is seeking clarification from the supplier. It is possible that the Panel would consider establishing a limit for formaldehyde/formalin.

Disodium Laureth Sulfosuccinate
Disodium Laureth-6 Sulfosuccinate
Disodium Laureth-9 Sulfosuccinate*
Disodium Laureth-12 Sulfosuccinate*
Disodium Deceth-5 Sulfosuccinate*
Disodium Deceth-6 Sulfosuccinate
Magnesium Laureth-3 Sulfosuccinate*
Disodium C12-14 Pareth-1 Sulfosuccinate*
Disodium C12-14 Pareth-2 Sulfosuccinate
Disodium C12-15 Pareth Sulfosuccinate*
Disodium Coceth-3 Sulfosuccinate*
Disodium Laneth-5 Sulfosuccinate*
Disodium C12-14 Sec-Pareth-3 Sulfosuccinate*
Disodium C12-14 Sec-Pareth-5 Sulfosuccinate*
Disodium C12-14 Sec-Pareth-7 Sulfosuccinate*
Disodium C12-14 Sec-Pareth-9 Sulfosuccinate*
Disodium C12-14 Sec-Pareth-12 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.

Ammonium Hectorites

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

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, which is the outer dead layer of cells that forms the surface of the skin. Components, such as lithium, in these ingredients are tightly bound and have no chance of leaching.

Disteardimonium Hectorite
Dihydrogenated Tallow Benzylmonium Hectorite*
Stearalkonium Hectorite
Quaternium-18 Hectorite

Dihydrogenated Tallow Benzylmonium Hectorite is not in current use (as indicated by *). Were this ingredient to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group

Citric Acid Group

Citric acid, its 12 inorganic salts, and its 20 alkyl esters listed below (total of 33 ingredients) were found safe in the present practices of use and concentration when formulated to be non-irritating.

For the 10 ingredients that are GRAS direct food additives, the focus of this safety assessment was on the non-oral toxicity of these ingredients. The CIR Expert Panel cited similarities in chemical structures, physicochemical properties, and functions and concentrations in cosmetics as support for including all 33 of the ingredients included in this safety assessment, and for extending the available toxicological data to support the safety of the entire group.

The Panel requested clarification of the ester structures. As currently defined in the *International Cosmetic Ingredient Dictionary and Handbook*, the monoester linkages are not identified as beta-carboxyl-only linkages. This raises the question whether some monoester linkages may be alpha-carboxyl linkages. Similarly, are all diester linkages on the beta-carboxyl groups only or are there alpha-carboxyl group linkages as well?

Citric Acid

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*
Triisocetyl Citrate
Triisopropyl Citrate*
Triisostearyl Citrate
Trilauryl Citrate*
Trioctyldodecyl 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 and that they would be formulated to be non-irritating.

Ethanolamine and Ethanolamine Salts

Ethanolamine and the 12 ethanolamine salts listed below were found safe in the current practices of use and concentration when formulated to be non-irritating, but these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

The CIR Expert Panel relied on the information available for ethanolamine in conjunction with previous safety assessments of the components of these ingredients, extrapolating those data to support the safety of the ethanolamine salts in this tentative amended safety assessment. The Panel noted that small amounts of diethanolamine could be present in ethanolamine and was concerned with the levels of free diethanolamine that could be present as an impurity. Hence the need to mention that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed. Also, because diethanolamine might be present as an impurity, the Panel re-iterated its discussion regarding the positive findings of a dermal carcinogenicity study of diethanolamine, noting that the carcinogenic effects reported in mice were not thought to be relevant to humans.

Ethanolamine
Ethanolamine HCl*
MEA-Benzoate*
MEA-Cocoate
MEA-Laureth Sulfate
MEA-Laureth-6 Carboxylate*
MEA-Lauryl Sulfate
MEA-PPG-6-Laureth-7 Carboxylate*
MEA-PPG-8-Steareth-7 Carboxylate*
MEA-Salicylate*
MEA-Sulfite*
MEA-Tallowate
MEA-Undecylenate*

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.

Ethanolamides

Isostearamide MEA and the other 27 ethanolamides listed below are safe in the current practices of use and concentration when formulated to be non-irritating.

The CIR Expert Panel originally considered a total of 50 ingredients in this tentative amended safety assessment, but further discussion identified characteristics of the chemical structure of 22 ingredients (now deleted) that were substantially different from the basic covalent, secondary amide structure of the other ingredients in this group, in which one of the nitrogen substituents is ethanol, or an ethanol residue, and the second is a carbonyl group.

Because the ethanolamides are secondary amides, the Panel was concerned that these ingredients can react with nitrosating agents to form N-nitroso compounds. Thus, ethanolamides should not be used in cosmetic products in which N-nitroso compounds may be formed. Additionally, if diethanolamine is present as an impurity, the levels of free diethanolamine must not exceed those considered safe by the Panel in the current safety assessment of diethanolamine.

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 the compounds will be bioavailable. Because reproductive and developmental toxicity data would enhance the data profile for this safety assessment, and biotransformation data and toxicokinetic data would also augment the data set, the Panel encouraged submission of such available data.

Isostearamide MEA*
Myristamide MEA
Stearamide MEA
Acetamide MEA
Azelamide MEA*
Babassuamide MEA*
Behenamide MEA*
C16-22 Acid Amide MEA*
Cocamide MEA
Cocamide Methyl MEA
Cocamidopropyl Betainamide MEA Chloride
Hydroxystearamide MEA*
Lactamide MEA
Lauramide MEA
Linoleamide MEA*
Oatamide MEA*
Oleamide MEA*
Oliveamide MEA*
Palm Kernelamide MEA*
Palmamide MEA*
Palmitamide MEA*
Pantothenamide MEA*
Peanutamide MEA
Ricinoleamide MEA
Sunfloweramide MEA*
Tallowamide MEA*
Trideceth-2 Carboxamide 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 and that they would be formulated to be non-irritating.

Galactomannans

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

While trigonella foenum-graecum seed extract and hydrolyzed trigonella foenum-graecum seed extract had been included in this group, additional data demonstrated that they have negligible polysaccharide content, and the CIR Expert Panel removed them from this safety assessment.

The Panel acknowledged the prevalence of IgE-mediated sensitization to a guar gum as reported in an occupational study. The Panel considered that such reactions are generally not attributable to exposures to carbohydrate moieties, and were likely the result of a combination of the carbohydrate plus residual plant protein and the inhalation of such material over a long period of time in an occupational setting. These data were not considered relevant to the use of galactomannans in cosmetics.

While these ingredients may be used in cosmetic sprays and aerosols, the predominantly non-respirable particle size produced from the use of such products, together with the small actual exposure in the breathing zone and the concentrations at which these ingredients are being used, the Panel agreed that inhalation would not be a significant route of exposure that might lead respiratory or systemic toxic effects.

Given the botanical sources of the galactomannans reviewed in this safety assessment, the Panel did state that restrictions on heavy metal and pesticide impurities will be included. While dioxin and pentachlorophenol (PCP) impurities have been detected in batches of cyamopsis tetragonoloba (guar) gum, the Panel noted that, given the absence of significant findings in repeated dose toxicity, teratogenicity, and carcinogenicity studies, these impurities are not of concern.

Caesalpinia Spinosa Gum
Caesalpinia Spinosa Hydroxypropyltrimonium Chloride*
Carboxymethyl Hydroxypropyl Guar*
Cassia Gum*
Cassia Hydroxypropyltrimonium Chloride
Ceratonia Siliqua Gum
Cyamopsis Tetragonoloba (Guar) Gum
Guar Hydroxypropyltrimonium Chloride
Hydrolyzed Ceratonia Siliqua Gum Extract*
Hydrolyzed Caesalpinia Spinosa Gum
Hydrolyzed Guar
C18-22 Hydroxyalkyl Hydroxypropyl Guar*
Hydroxypropyl Guar
Hydroxypropyl Guar Hydroxypropyltrimonium Chloride
Locust Bean Hydroxypropyltrimonium Chloride
Trigonella Foenum-Graecum Hydroxypropyltrimonium Chloride*

Were the ingredients 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 this group.

Synthetic Fluorphlogopite

Synthetic fluorphlogopite is safe in the present practices of use and concentration in cosmetics.

The CIR Expert Panel reviewed additional information provided including genotoxicity, inhalation toxicity, dermal irritation and sensitization, and phototoxicity/photosensitization data.

This ingredient is a synthetic mimic of a mica-type mineral with fluorine substituents in magnesium aluminum silicate sheets weakly bound together by layers of potassium ions. The Panel previously reviewed the extensive data sets regarding the safety of magnesium aluminum silicate and related clay ingredients and found them safe for use in cosmetics. This ingredient is different because it contains two fluorine atoms bound to each aluminum atom in the sheet structure. While the fluorine is ionically bound, it is unlikely to dissociate. While no data were available on dermal penetration, the CIR Expert Panel viewed these large sheets of synthetic fluorphlogopite to be unlikely to pass the stratum corneum, which is the outer dead layer of cells that forms the surface of the skin.

Insufficient Data Announcement

For insufficient data announcements, 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 22, 2012, or sooner if possible.*** *These ingredient reports may be scheduled for review by the CIR Expert Panel at its* ***March 5-6, 2012*** *meeting.*

Dialkyl Malates

The CIR Expert Panel made a request for additional data for diisostearyl malate and the other 5 dialkyl malates listed below. The data needs include: genotoxicity in a mammalian assay system and a 28-day dermal toxicity study (with the expectation that data from such a study would include dermal penetration). In addition, the Panel noted that the case literature for octyldodecanol includes reports of allergic reactions. While dioctyldodecyl malate is not in current use, the Panel noted that dermal irritation/sensitization data on this ingredient may be useful, if available.

Initially, this group encompassed both malic and tartaric acid and their salts and esters. The Panel determined that the tartaric acid esters, as dihydroxy succinic acid (tartaric acid) derivatives, were sufficiently different from the monohydroxy succinic acid (malic acid) to limit this safety assessment to only the widely used malate esters. The Panel also determined to not include malic acid and sodium malate. Three Ingredients are not in current use (indicated by *).

Dibutyloctyl Malate*
Di-C12-13 Alkyl Malate
Diethylhexyl Malate
Diisoamyl Malate*
Diisostearyl Malate
Dioctyldodecyl Malate*

Re-Reviews

Methyldibromo Glutaronitrile – not reopened

The CIR Expert Panel reaffirmed the original conclusion that methyldibromo glutaronitrile is safe as used in rinse-off products and safe at $\leq$ 0.025% in leave-on products.

The Expert Panel reviewed new data available since the original safety assessment was published, including a large number of dermal irritation and sensitization studies. The Panel noted that the European Commission had banned the ingredient from both leave-on and rinse-off products due to increased reports of sensitivity. However, the Panel was of the opinion that many, if not most, reports of sensitization in patch test studies likely are due to testing at high concentrations such that the reactions observed are actually irritation responses. Based on this information, the Expert Panel determined to not reopen this safety assessment.

Polyvinyl Acetate – not reopened

The Expert Panel reaffirmed the original conclusion that polyvinyl acetate is safe as a cosmetic ingredient in the present practice of use.

The Panel noted that the number of uses and the use concentration have increased. Current data indicate uses at concentrations up to 47%. However, the original safety assessment details a human repeat insult patch study in which polyvinyl acetate was tested at a concentration of 50% with no allergic or irritation responses. Based on this observation, the Panel determined that the new current usage levels would be considered safe and determined to not reopen this safety assessment.

Re-review summaries - The CIR Expert Panel approved the re-review summaries for 4-Chlororesorcinol and Glutaral.

121st Meeting Notes

Director's Report

Dr. Andersen introduced CIR's new Deputy Director, Dr. Lillian Gill, shown in the photo to the right, who has joined CIR after a 35-year career at the U.S. Food and Drug Administration.

He also remarked on the great strides towards transparency that are at the heart of the new CIR website. He noted that CIR expects to again have 3 supplemental issues of the *International Journal of Toxicology* appear this year. He expressed concern that it is becoming increasingly difficult to schedule report reviews over the year, and between meetings, in a way that accommodates the need to provide 60-day public comment periods, the expectation that CIR would incorporate all such input from interested parties into a revised report, and the need to provide material to the Panel in a timely and effective manner.

CIR Website Previewed

Kevin Fries, CIR's Information Services Manager previewed the new CIR website. While the improved aesthetics and the updated logo (shown here) provide a more pleasing site for everyone, he suggested that the important changes relate to ease of navigation and material provided for easy access.

Mr. Fries highlighted the easy availability of Panel review material by Panel members, industry, dermatologists, and consumers alike, marking another step in transparency for the CIR program.

CIR Director receives award

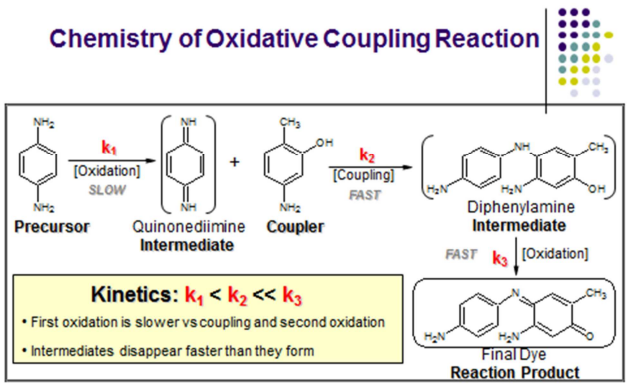
At the Food and Drug Law Institute's Annual Awards and Holiday Reception on December 6th, CIR Director, Dr. Alan Andersen, was presented with the 2011 FDLI Distinguished Service and Leadership Award. He was one of 4 recipients recognized for their contributions to the food and drug law field, to the food and drug law community, and to FDLI.

In his remarks, Dr. Andersen highlighted CIR's 35 years of operation as an independent safety assessment program founded by the Personal Care Products Council (PCPC), with the support of FDA and the Consumer Federation of America.

Hair dye chemistry presentation – Dr. Julie Skare

Julie Skare, Ph.D., from Proctor and Gamble currently serves as the Chair, Hair Colorants Technical Committee, Personal Care Products Council. She reviewed the chemistry of both oxidative and semi-permanent hair dyes.

Dr. Skare explained that oxidative hair dye formulations combine precursors and coupling agents with an oxidizing agent, such as hydrogen peroxide, to produce reaction products, which are the actual hair colorants. Other components of the hair dye formulation allow the hair to swell and the reaction products to adsorb into the hair shaft. When the formulation is rinsed, the hair shaft returns to its normal size, trapping the colorant. The three main classes of precursors are: p-phenylenediamines, p-aminophenols, and heterocyclic diamines. The five main classes of couplers are: resorcinols, m-aminophenols, m-phenylenediamines, pyridines and naphthols. In each case, the reaction proceeds through a series of reaction intermediates. Since the kinetics of formation of the reaction intermediates from the precursor is slow and the reaction of the intermediate with the coupler has fast reaction kinetics, the reaction intermediate does not accumulate. Likewise, the color intermediate undergoes a fast secondary oxidation to form the final color, so that the intermediates do not accumulate. She used the example shown below to illustrate the point.



While reaction intermediates may be formed, human exposure is to the precursors and coupling agents and to reaction products, not to the reaction intermediates. The exposures to the precursors and couplers are low (they are consumed in the color forming reaction), and the exposures to reaction products are even lower (they are adsorbed into the hair shaft itself and physically retained there). Therefore, safety assessments of oxidative hair dyes are driven by the toxicological evaluation of the ingredients (i.e. precursors and coupling agents), more than by the reaction products formed during use, and not at all by reaction intermediates.

Semi-permanent hair dyes are preformed colors that become associated with the hair shaft, but since there is much less swelling of the hair shaft, they are not as tightly bound and a little of the color will be lost from the hair with each washing - hence, the semi-permanent nature of these formulations.

Examples of these colorants include: nitro-phenylenediamines, amino-nitrophenols, azo dyes, and anthraquinone dyes. The safety assessment of these hair dyes are driven by the toxicological evaluation of the colorants themselves.

Dr. Skare went on to describe studies done on representative oxidative hair dye reaction products to determine likely dermal penetration. In each case the dermal penetration of the reaction product was substantially lower than the dermal penetration of the precursors or the couplers – by as much as 3 orders of magnitude. She also described an effort to evaluate reaction products in genotoxicity assays. In vitro test used included Ames bacterial assays, hprt

locus mutation assays and micronucleus assays in mammalian cells. In vivo testing included micronucleus assays and unscheduled DNA synthesis in animals. While some positive findings were reported using in vitro assays, no evidence of genotoxicity was found in vivo.

Cosmetics aerosols

The CIR Expert Panel reaffirmed the view that the particles produced from the use of cosmetics sprays and aerosols are predominantly non-respirable, and, given the small actual exposure in the breathing zone, are not usually a significant route of exposure. That said, the Panel acknowledged that the concentration at which a particular ingredient is used, the availability of inhalation exposure data, and the other safety test data that are available also must be factored into the discussion.

This reaffirmation resulted from the Panel's review of the updated aerosols precedents document, which explains the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products that may be sprayed or aerosolized. The document also provides guidance to CIR staff for preparing safety assessment reports for such ingredients.

The Panel emphasized that, while this thinking likely applies to most circumstances, there may be situations in which the respiratory tract is understood to be at risk from exposures to cosmetic ingredients in certain product types and that such risk would determine the Panel's conclusion. The example was cited of formaldehyde and methylene glycol in hair smoothing products.

Apropos of this thinking, the Panel revised the precedents document to state, explicitly, that inhaled chemicals deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract may cause toxic effects in these regions, depending on their chemical and other properties, and that the potential for toxic effects is not limited to respirable particles deposited in the lungs. The Panel noted that, while the aerodynamic equivalent diameters of the particles/droplets of an aerosol are important for determining where the particles/droplets will be deposited in the respiratory tract, the chemical and other properties of the particles/droplets will determine whether they will cause toxic effects where they are deposited.

The Panel also reviewed the conservative inhalation exposure estimates submitted by the CIR SSC to illustrate the small contributions that incidental inhalation exposures are likely to make to overall exposures to cosmetic product ingredients, and indicated that these estimates should be incorporated into the aerosols precedents document as examples. The Panel directed that the revised document should be posted on the CIR Website, first to solicit public comments on the document, and then to provide interested parties with easy access to the background information, the location of which would be included in relevant ingredient safety assessments.

Two Reports Tabled

Ginseng Root-derived Ingredients

The CIR Expert Panel tabled discussion of this safety assessment to allow additional data to be incorporated.

While the types of components and concentrations that may be expected to be found in ingredients derived from ginseng root generally were not considered to present a safety concern, the CIR Expert Panel did note that the case literature suggested potential endocrine activity (e.g., postmenstrual bleeding) associated with use of a ginseng face cream. While information on the specific ginseng ingredient and concentration in this face cream was not available during the discussion, the Panel was concerned that composition information on this product should be obtained and that available data on endocrine effects of ginseng and/or ginseng root components should be added to the report.

In addition to product information and data on possible endocrine activity, because the evidence of endocrine activity in the case literature appears to be related to ingestion, the Panel suggested that information on dermal penetration may become important. Interested parties were encouraged to provide available dermal penetration data.

The Panel noted that pulegone has been reported to be a component of the root essential oil derived from *Panax quinquefolium*. Based on concerns regarding pulegone toxicity, the Panel noted that pulegone likely would be restricted to ≤ 1% in Panax Quinquefolium Root Extract.

The 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

Polyquaternium-22 and -39

The CIR Expert Panel tabled discussion of this safety assessment to expand the report to include other polyquaternium ingredients.

The Panel considered that the evaluation of the safety of all polyquaternium ingredients in the *International Cosmetic ingredient Dictionary and Handbook* would substantially focus on the similarities of this qroup of ingredients, such as large molecular weight and ionic nature of the quaternary nitrogen moiety. The Panel recognized that these ingredients may be comprised of different building blocks and that an expanded group would have to consider the possibility of unreacted monomers. For example, the Expert Panel is requesting that industry provide information on the acrylamide monomer content of polyquaternium-22 and polyquaternium-39. This question would also apply to any polyquaternium ingredient for which one of the building blocks is acrylamide. Different residual monomer questions would exist for polyquaternium-65, for example, which is comprised of 2-methyacryloyloxyethylphosphorylcholine, butyl methacrylate, and sodium methacrylate monomers.

Scientific Literature Reviews

- **Previously posted on the CIR website (www.cir-safety.org) - comment period closed - will be considered for the next CIR Expert Panel meeting**
  - Bis-diglyceryl polyacyladipates
  - Cucumber-derived ingredients
  - Amino Acids

- **Currently posted on the CIR website (www.cir-safety.org) for comment**
  - Borosilicate glasses
  - Chlorphenesin
  - Microbial polysaccharides
  - Nylon polymers

- **Scientific Literature Reviews under development (to be issued in 2012).**
  - Dimethicone crosspolymers
  - Fatty acid amidopropyl dimetylamines
  - Methyl glucose ethers and esters
  - Tin oxide
  - Vitis vinifera-derived ingredients

Next CIR Expert Panel Meeting - Monday and Tuesday, March 5-6, 2012 at the Renaissance Hotel, DuPont Circle, 1143 New Hampshire Ave., NW, Washington, DC 20037 - Please contact Carla Jackson (jacksonc@cir-safety.org) at CIR before the meeting if you plan to attend.