Announcement

Cosmetic Ingredient Review Expert Panel
134th Meeting (March 16-17, 2015) - Findings

March 20, 2015

- **Final Safety Assessments**
  - **Ceramides – 23 ingredients**
  - **PEG Diesters – 55 ingredients**
  - **Lecithin and Other Phosphoglycerides – 17 ingredients**
  - **Sodium Benzotriazolyl Butylphenol Sulfonate – 1 ingredient**

- **Tentative Safety Assessments**
  - ***Centella asiatica*-Derived Ingredients – 9 ingredients**
  - **PEGs Cocamine – 47 ingredient**
  - **Polyenes – 26 ingredients**
  - **Polysorbates – 79 ingredients**

- **Insufficient Data Announcement**
  - **Citrus Fruit-Derived Ingredients – 80 ingredients**

- **Re-reviews**
  - **Bisabolol – not reopened**
  - **Hydroxystearic acid – reopened**
  - **Isostearamidopropyl Morpholine Lactate – not reopened**
  - **Nonoxynols – reopened**

- **134th Meeting Notes**
  - **Director's Report**
  - **Reports Tabled**
    - **Polymerized Tetramethylcyclotetrasiloxane – 3 ingredients**
  - **Scientific Literature Reviews posted on the CIR website**
  - **Scientific Literature Reviews under development**
  - **Re-reviews for the next Panel meeting**
  - **Ingredient strategies – 4 ingredients**
  - **Draft 2016 ingredient review priorities – comments sought**
  - **Next CIR Expert Panel Meeting – Monday and Tuesday, June 15-16, 2015**

Final Safety Assessments

Final safety assessments and final amended safety assessments will be posted on the CIR website at www.cir-safety.org. Unpublished data cited as references in CIR safety assessments are available for review. 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.

Ceramides

The Panel issued a final safety assessment with the conclusion that the following 23 ceramides are safe in cosmetics in the present practices of use and concentration:

ceramide 1
ceramide 2
ceramide 3
ceramide 4*
ceramide 5*
ceramide 1A

ceramide 6 II
ceramide AP
ceramide EOP
ceramide EOS
ceramide NP
ceramide NG*
ceramide NS
ceramide AS*
ceramide NS dilaurate*
caprooyl phytosphingosine
caprooyl sphingosine
hydroxypalmitoyl sphinganine
2-oleamido-1,3-octadecanediol
caproyl sphingosine*
hydroxylauroyl phytosphingosine*
hydroxycapryloyl phytosphingosine*
hydroxycaproyl phytosphingosine*

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

The Panel noted that there was a screening reproductive and developmental toxicity study on 2-oleamido-1,3-octadecanediol, however there was no data on carcinogenicity. The Panel considered the negative results of a reproductive and developmental toxicity study in rats and of in vitro genotoxicity assays, as well as the findings of no systemic toxicity at high doses in single and repeated oral dose animal studies, little to no irritation in ocular and dermal animal studies, no dermal irritation in human studies, and no dermal sensitization in multiple animal studies to support their conclusion for these ingredients.

The names of ceramide ingredients have changed recently. For example, the INCI name, ceramide 1 has been retired and replaced by the name ceramide EOP. For an interim period, products on the market may be labelled with either name, ceramide 1 or ceramide EOP, although both names refer to the same ingredient.

The Panel determined that these ceramide ingredients are safe as used, assuming that the ingredients are not derived from bovine central nervous system tissues.

PEG Diesters

The Panel issued a final amended safety assessment with the conclusion that 55 PEG diesters are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating. The ingredients in this report are:

PEG-150 dibehenate*
PEG-3 dicaprylate/caprate*
PEG-4 dicocoate*
PEG-8 dicocoate
PEG-4 diheptanoate
PEG-2 diisononanoate
PEG-2 diisostearate*
PEG-3 diisostearate*
PEG-4 diisostearate*
PEG-6 diisostearate
PEG-8 diisostearate
PEG-12 diisostearate
PEG-90 diisostearate
PEG-175 diisostearate
PEG-2 dilaurate*
PEG-4 dilaurate
PEG-6 dilaurate*
PEG-8 dilaurate
PEG-12 dilaurate*
PEG-16 dilaurate*
PEG-20 dilaurate*
PEG-32 dilaurate*
PEG-75 dilaurate*
PEG-150 dilaurate*
PEG-2 dioleate*
PEG-3 dioleate*
PEG-4 dioleate*
PEG-6 dioleate*
PEG-8 dioleate
PEG-10 dioleate*
PEG-12 dioleate
PEG-20 dioleate*
PEG-32 dioleate*
PEG-75 dioleate*
PEG-150 dioleate*
PEG-3 dipalmitate*
PEG-2 distearate
PEG-3 distearate
PEG-4 distearate
PEG-6 distearate
PEG-8 distearate
PEG-9 distearate*
PEG-12 distearate
PEG-20 distearate*
PEG-32 distearate*
PEG-40 distearate*
PEG-50 distearate
PEG-75 distearate*
PEG-120 distearate
PEG-150 distearate
PEG-175 distearate
PEG-190 distearate*
PEG-250 distearate
PEG-8 ditallate*
PEG-12 ditallate*

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

In this safety assessment, PEG-150 distearate was reported to have the greatest number of uses at 690 (an increase from 187 in 1996). Most of these uses are in bath and personal cleansing products and shampoos. PEG-150 distearate was reported to have the greatest concentration of use at up to 33.2% (an increase from 5% in 1995); the highest concentration of use was in skin cleansing products. PEG-4 dilaurate and PEG-8 dilaurate were each reported to be used at concentrations up to 25% in 1984, and are currently used at concentrations up to 12% and 15%, respectively.

Unlike PEG-8 dioleate and PEG-8 dilaurate, 5% PEG-12 dioleate enhanced the dermal penetration of ketoprofen in a study using nude mice. The Panel noted that formulators should be aware of the potential for enhancing the dermal penetration of other ingredients in cosmetic formulations that contain PEG diesters.

Lecithin and Other Phosphoglycerides

The Panel issued a final safety assessment with the conclusion that lecithin and 16 other phosphoglyceride ingredients are safe in the present practices of use and concentration. This report includes data from the 2001 published CIR final report on the safety assessment of lecithin and hydrogenated lecithin, and the new conclusion supersedes the conclusion stated in the 2001 published final report.

The ingredients in this report are:

lecithin
hydrogenated lecithin
lysolecithin
hydrogenated lysolecithin*

phospholipids
hydrolyzed phospholipids*
phosphatidic acid*
lysophosphatidic acid
phosphatidylglycerol*
lysophosphatidylglycerol*
phosphatidylserine*
ammonium phosphatidyl rapeseedate*
phosphatidylcholine
hydrogenated phosphatidylcholine*
hydrogenated lysophosphatidylcholine*
lysophosphatidylethanolamine*
phosphatidylinositol*

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

The Panel published a final report in 2001 with the conclusion that lecithin and hydrogenated lecithin are safe as used in rinse-off products and safe for use in leave-on products at concentrations ≤ 15%, the data are insufficient to determine the safe use in cosmetic products where lecithin and hydrogenated lecithin are likely to be inhaled, and lecithin and hydrogenated lecithin should not be used in cosmetic products in which *N*-nitroso compounds may be formed. At the March 2015 meeting, the Panel determined that the restrictions were no longer relevant because new data and extensive clinical experience suggest safe use at the current highest reported maximum use concentration of 50% in leave-on products. Although some phospholipids have the potential to produce physiological effects, such effects are not reproduced by application of phospholipids to the skin.

Concerns about the possibility that incidental inhalation exposure to lecithin and hydrogenated lecithin in products that are sprayed or in powder form were resolved by considering the results of an inhalation toxicity study demonstrating that, under the conditions of use described, the likely airborne particle size distributions and concentrations of these ingredients in the breathing zone would not lead to local respiratory or systemic effects if incidentally inhaled. Additionally, the Panel noted that lecithin is an inactive ingredient in FDA-approved aerosolized drug products.

In the previous safety assessment, concerns about the formation of *N*-nitroso compounds in cosmetic products containing lecithin and hydrogenated lecithin were based on experimental conditions that do not represent plausible use conditions. For example, lecithin has been reported to be metabolized to choline by bacterial phospholipases in a model system, and the released choline can be dealkylated to dimethylamine, which is N-nitrosatable in the presence of nitrate. The Panel has determined that these experimental conditions do not reflect ingredient use in cosmetic products.

Because of concerns about potential transmission of bovine spongiform encephalopathy (BSE) and other diseases, the Food and Drug Administration does not permit cosmetic products to contain ingredients made from bovine central nervous system tissue and other risk-specific materials obtained from cattle. Thus, the Panel determined that lecithin and other phosphoglycerides are safe as used, noting that ingredients are not derived from bovine central nervous system tissues or other risk materials.

Sodium Benzotriazolyl Butylphenol Sulfonate

The Panel issued a final safety assessment with the conclusion that sodium benzotriazolyl butylphenol sulfonate is safe as used in cosmetics.

This ingredient is reported to function as a light stabilizer (i.e., protecting the product from chemical or physical deterioration induced by light) in cosmetics. Data from robust summaries found on the European Chemicals Agency (ECHA) website are included in this report.

Sodium benzotriazolyl butylphenol sulfonate was reported to be used in 68 leave-on products, 380 rinse-off products, and 29 products for the bath. The maximum concentration of use reported was 0.17% in leave-on products, specifically in nail polish and enamels.

Tentative Safety Assessments

Tentative safety assessments will be posted on the CIR website at www.cir-safety.org on or before ***March 27, 2015****. 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, and are available for review by any interested party. Please submit data and/or comments to CIR by* ***May 27, 2015, or sooner if possible.*** *These reports may be scheduled for review by the CIR Expert Panel at its* ***June 15-16, 2015*** *meeting.*

***Centella asiatica* – Derived Ingredients**

The Panel issued a tentative report for public comment with the conclusion that centella asiatica leaf extract and centella asiatica meristem cell culture are safe in the present practices of use and concentration in cosmetics when formulated to be non-sensitizing, and that the available data are insufficient for evaluating the safety of the following 7 ingredients in cosmetic products:

centella asiatica extract
centella asiatica callus culture
centella asiatica flower/leaf/stem extract
centella asiatica leaf cell culture extract
centella asiatica leaf water
centella asiatica meristem cell culture extract
centella asiatica root extract

The data requested are as follows:

- Method of manufacture, composition, and impurities data on the ingredients listed above
- Irritation and sensitization data for all ingredients
- 28-day dermal toxicity data on centella asiatica extract or centella asiatica root extract. If it is determined that centella asiatica root extract is a component of centella asiatica extract, only data on centella asiatica extract are needed.

Botanical ingredients, derived from natural plant sources, are complex mixtures. The Panel was concerned that cosmetics containing these ingredients be formulated to be non-sensitizing because the levels of potentially sensitizing constituents in the ingredients can be quite variable (depending on plant growth conditions, extraction methods, and other factors), and the data available from sensitization tests may not represent the complete spectrum of concentrations of such constituents in the ingredients as used in cosmetic products. In addition, the Panel was concerned that the concentrations of potentially sensitizing constituents should not exceed levels of concern in formulations containing ingredients from multiple plant species that each can contribute such constituents to the overall formulations.

The cell-mediated immune response to *Centella asiatica* extracts differs depending on the method of ingredient extraction. For example, an aqueous extract of *Centella asiatica* stimulated cytokine production, whereas *centella asiatica* in ethanol extract inhibited cytokine production. The Panel noted that findings such as these support the need for chemical characterization data on *Centella asiatica*-derived ingredients that are used in cosmetic products.

The Panel also noted the data indicating that centella asiatica leaf extract was toxic to the reproductive system of male rats, and concluded that the level of centella asiatica leaf extract and centella asiatica meristem cell culture used in cosmetics should be below the threshold of toxicologic concern for that reproductive toxicity.

PEGs Cocamine and Related Ingredients

The Panel issued a tentative amended report for public comment with the conclusion that the following 47 PEGs cocamine and related ingredients are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating:

PEG-2 cocamine
PEG-3 cocamine*
PEG-4 cocamine*
PEG-5 cocamine
PEG-8 cocamine*
PEG-10 cocamine*
PEG-12 cocamine*
PEG-15 cocamine
PEG-20 cocamine*
PEG-2 hydrogenated tallow amine*
PEG-5 hydrogenated tallow amine
PEG-8 hydrogenated tallow amine
PEG-10 hydrogenated tallow amine*
PEG-15 hydrogenated tallow amine*
PEG-20 hydrogenated tallow amine*
PEG-30 hydrogenated tallow amine*
PEG-40 hydrogenated tallow amine*
PEG-50 hydrogenated tallow amine*
PEG-2 lauramine*
PEG-2 oleamine
PEG-5 oleamine*
PEG-6 oleamine*
PEG-10 oleamine*
PEG-15 oleamine*
PEG-20 oleamine*
PEG-25 oleamine*
PEG-30 oleamine*
PEG-12 palmitamine*
PEG-2 rapseedamine
PEG-2 soyamine
PEG-5 soyamine
PEG-8 soyamine*
PEG-10 soyamine*
PEG-15 soyamine*
PEG-2 stearamine*
PEG-5 stearamine*
PEG-10 stearamine*
PEG-15 stearamine*
PEG-50 stearamine*
PEG-2 tallow amine
PEG-7 tallow amine*
PEG-11 tallow amine*
PEG-15 tallow amine*
PEG-20 tallow amine*
PEG-22 tallow amine*
PEG-25 tallow amine*
PEG-30 tallow amine*

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

The Panel noted that the tallow moieties of several of the selected analogs, including PEG-2 tallow amine, have greater degrees of unsaturation and, consequently, greater susceptibility to epoxidation than the fatty acid moieties of the PEGs cocamine and other related ingredients. Thus, the incorporation of the genotoxicity and repeated-dose toxicity data available for these analogs represents a conservative approach to the read-across analysis of the ingredient group. The equivocal results of a local lymph node assay (LLNA) for dermal sensitization of PEG-2 hydrogenated tallow amine were confounded by the irritant properties of the ingredient and difficult to interpret, and were not consistent with the negative results of a guinea pig maximization test of this ingredient. The Panel also noted that exposure durations and frequencies for the smaller ingredients in this group (i.e., PEG-2, 3, 4, and 5 cocamine and related ingredients) would be relatively low, because these ingredients are used predominantly in rinse-off hair-coloring products.

Polyenes

The Panel issued a tentative report for public comment with the conclusion that the following 26 polyenes are safe in cosmetics in the present practices of use and concentration.

butene/propylene copolymer*
butylene/ethylene copolymer
butylene/ethylene/propylene copolymer
decene/butene copolymer
ethylene/octene copolymer*
ethylene/propylene copolymer
hydrogenated poly(C6-12 olefin)
hydrogenated poly(C6-14 olefin)
hydrogenated poly(C6-20 olefin)
hydrogenated polybutene*
hydrogenated polydecene
hydrogenated polydodecene*
hydrogenated polyisobutene
isobutylene/isoprene copolymer*
isoprene/pentadiene copolymer*
polybutene
poly(C4-12 olefin)*
poly(C6-14 olefin)*
poly(C20-28 olefin)*
poly(C30-45 olefin)
polydecene
polyethylene
polyisobutene
polyisoprene
polypentene*
polypropylene

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

The Panel noted low systemic toxicity at high doses in single-dose and the repeated-dose animal studies, no teratogenic or carcinogenic effects in animal studies, and no genotoxicity in in vitro and in vivo studies of polyenes. The data indicated use concentrations as high as 95% in lipsticks. However, a human dermal sensitization study of 100% hydrogenated polyisobutene was negative, and no irritation or sensitization was observed in multiple tests when other polyene ingredients were used. The Panel noted that, although molecular weights of some of the ingredients are in a range that could be dermally absorbed, the lack of heteroatomic functional groups substantially limits solubility and would prevent significant absorption. The lack of such functional groups also limits interactions with other biomolecules and probably accounts for the apparent biological inertness of these ingredients in this group.

Although data were not available on the UV absorption of polyenes, because none of the polymer ingredients contain chromophores, the Panel expressed no concern that these ingredients would cause adverse effects from UV exposure.

Polysorbates

The Panel issued a tentative report for public comment with the conclusion that the following 79 polysorbates are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating. This report combines the polysorbates from the final reports published in 1984, 2000, and 2001 and reflects a change from the Panel's previous safe-as-used conclusion. These ingredients mostly function as surfactants in cosmetics. Four of these ingredients have had name changes since their original safety assessments.

The ingredients in this report are:

polysorbate 20
polysorbate 21
polysorbate 40
polysorbate 60
polysorbate 61
polysorbate 65
polysorbate 80
polysorbate 81
polysorbate 85
PEG-20 sorbitan cocoate
PEG-40 sorbitan diisostearate
PEG-2 sorbitan isostearate*
PEG-5 sorbitan isostearate*
PEG-20 sorbitan isostearate
PEG-40 sorbitan lanolate
PEG-75 sorbitan lanolate*
PEG-10 sorbitan laurate
PEG-40 sorbitan laurate
PEG-44 sorbitan laurate
PEG-75 sorbitan laurate
PEG-80 sorbitan laurate
PEG-3 sorbitan oleate
PEG-6 sorbitan oleate
PEG-20 sorbitan oleate*
PEG-40 sorbitan oleate*
PEG-80 sorbitan palmitate*
PEG-40 sorbitan perisostearate*
PEG-40 sorbitan peroleate
PEG-3 sorbitan stearate
PEG-4 sorbitan stearate*
PEG-6 sorbitan stearate
PEG-40 sorbitan stearate
PEG-60 sorbitan stearate*
PEG-30 sorbitan tetraoleate
PEG-40 sorbitan tetraoleate
PEG-60 sorbitan tetraoleate
PEG-60 sorbitan tetrastearate*
PEG-4 sorbitan triisostearate*
PEG-20 sorbitan triisostearate*
PEG-160 sorbitan triisostearate
PEG-2 sorbitan trioleate*
PEG-18 sorbitan trioleate
PEG-3 sorbitan tristearate*
sorbeth-2 beeswax*
sorbeth-6 beeswax
sorbeth-8 beeswax*
sorbeth-20 beeswax
sorbeth-2 cocoate*
sorbeth-2 hexacaprylate/caprate*
sorbeth-12 hexacocoate*
sorbeth-2 hexaisostearate*
sorbeth-2 hexalaurate*
sorbeth-2 hexaoleate*
sorbeth-40 hexaoleate (PEG-40 sorbitol hexaoleate)*
sorbeth-50 hexaoleate (PEG-50 sorbitol hexaoleate)*
sorbeth-6 hexastearate*
sorbeth-150 hexastearate*
sorbeth-3 isostearate*
sorbeth-6 laurate*
sorbeth-2/oleate/dimer dilinoleate crosspolymer*
sorbeth-20 pentaisostearate*
sorbeth-30 pentaisostearate*
sorbeth-40 pentaisostearate*
sorbeth-50 pentaisostearate*
sorbeth-40 pentaoleate*
sorbeth-20 tetraisostearate*
sorbeth-30 tetraisostearate
sorbeth-40 tetraisostearate*
Sorbeth-50 tetraisostearate*
sorbeth-4 tetraoleate
sorbeth-6 tetraoleate
sorbeth-30 tetraoleate
sorbeth-40 tetraoleate
sorbeth-60 tetraoleate
sorbeth-30 tetraoleate laurate (PEG-30 sorbitol tetraoleate laurate)*
sorbeth-60 tetrastearate (PEG-60 sorbitol tetrastearate)*
sorbeth-3 tristearate*
sorbeth-160 tristearate*
sorbeth-450 tristearate*

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

At the time of the original safety assessment of sorbeth-6 beeswax, sorbeth-8 beeswax, and sorbeth-20 beeswax in 2001, the Panel recommended that cosmetic formulations containing the PEG moiety not be used on damaged skin. Since then, PEGs have been re-reviewed and the Panel has removed this caveat for these, and all other PEG-containing cosmetic ingredients.

Insufficient Data Announcement

For this insufficient data announcement, interested persons are given an opportunity to comment, provide information and/or request an oral hearing before the CIR Expert Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, and are available for review by any interested party. Please submit data and/or comments to CIR by ***May 27, 2015, or sooner if possible****. This report is scheduled for review by the CIR Expert Panel at its* ***June 15-16, 2015*** *meeting.*

Citrus Fruit-derived Ingredients

The Panel issued an insufficient data announcement on the following 80 ingredients:

citrus aurantifolia (lime)/citrus limon (lemon) fruit water
citrus aurantifolia (lime) fruit
citrus aurantifolia (lime) fruit extract
citrus aurantifolia (lime) fruit water
citrus aurantifolia (lime) juice
citrus aurantium amara (bitter orange) fruit extract
citrus aurantium amara (bitter orange) fruit juice extract
citrus aurantium bergamia (bergamot) fruit extract
citrus aurantium bergamia (bergamot) fruit oil
citrus aurantium bergamia (bergamot) fruit water
citrus aurantium dulcis (orange) fruit extract
citrus aurantium dulcis (orange) fruit powder
citrus aurantium dulcis (orange) fruit water
citrus aurantium dulcis (orange) juice
citrus clementina fruit extract
citrus clementina juice
citrus depressa fruit extract
citrus depressa fruit water
citrus glauca fruit extract
citrus grandis (grapefruit) fruit extract
citrus grandis (grapefruit) fruit/peel water
citrus grandis (grapefruit) fruit water
citrus grandis (grapefruit) juice
citrus grandis/paradisi fruit water
citrus hassaku fruit extract
citrus hassaku/natsudaidai fruit juice
citrus hassaku/natsudaidai fruit powder
citrus iyo fruit extract
citrus iyo fruit water
citrus jabara juice
citrus japonica fruit extract
citrus junos fruit extract
citrus junos fruit juice
citrus junos fruit oil
citrus junos fruit powder
citrus junos fruit water
citrus limon (lemon) fruit extract
citrus limon (lemon) fruit oil
citrus limon (lemon) fruit powder
citrus limon (lemon) fruit water
citrus limon (lemon) juice
citrus limon (lemon) juice extract
citrus limon (lemon) juice powder
citrus madurensis fruit extract
citrus madurensis fruit juice
citrus medica vulgaris fruit extract
citrus nobilis (mandarin orange) fruit extract
citrus nobilis (mandarin orange) fruit juice
citrus paradisi (grapefruit) fruit extract
citrus paradisi (grapefruit) fruit water
citrus paradisi (grapefruit) juice
citrus reticulata (tangerine) fruit
citrus reticulata (tangerine) fruit extract
citrus reticulata (tangerine) fruit water
citrus shunkokan fruit extract
citrus sinensis (orange) fruit extract
citrus sinensis (orange) fruit water
citrus sphaerocarpa fruit juice
citrus sudachi fruit extract
citrus sudachi fruit juice
citrus tachibana/reticulata fruit juice
citrus tamurana fruit extract
citrus tangelo fruit juice
citrus tangelo fruit powder
citrus tangerina (tangerine) fruit
citrus tangerina (tangerine) fruit water
citrus tankan fruit extract
citrus tankan fruit water
citrus unshiu/citrus reticulata/citrus iyo fruit water
citrus unshiu fruit extract
citrus unshiu fruit juice
citrus unshiu fruit juice ferment extract filtrate
citrus unshiu fruit oil
citrus unshiu fruit powder
citrus unshiu fruit water
citrus unshiu/sinensis/reticulata fruit extract
defatted citrus unshiu fruit
hydrolyzed citrus aurantium dulcis fruit extract
microcitrus australasica fruit extract
microcitrus australis fruit extract

The data requested are as follows:

- Method of manufacture
- Chemical composition and impurities data
- Irritation and sensitization data, specifically human repeated insult patch tests (HRIPT) on citrus aurantium dulcis (orange) fruit water, citrus limon (lemon) fruit extract, and citrus grandis (grapefruit) fruit extract at maximum use concentrations
- Confirmation from the Research Institute for Fragrance Materials (RIFM) that citrus aurantium bergamia (bergamot) fruit oil, citrus junos fruit oil, citrus junos fruit water, citrus natsudaidai flower water, citrus reticulata (tangerine) fruit water, and citrus unshiu/citrus reticulata/citrus iyo fruit water has, or will be, assessed by RIFM.
- Confirmation on which species of citrus fruit are *not* Generally Recognized as Safe (GRAS) by the Food and Drug Administration (FDA)

Re-reviews

Bisabolol – not reopened

The Panel reaffirmed the original conclusion that bisabolol is safe as used in cosmetic formulations.

The frequency of use has increased from 184 reported uses in 1997 to 999 reported uses in 2015, with a majority of uses in leave-on products. The reported maximum use concentration has not increased.

The Panel noted case reports of positive reactions in pediatric atopic dermatitis patients during irritation testing with bisabolol. In these studies, the irritation was observed when testing on damaged skin. A photosensitization study that was described in the 1999 safety assessment of bisabolol indicated that bisabolol at concentrations up to 15% was not a sensitizer. The Panel also noted a study examining the skin-lightening effect of bisabolol on the skin of Asian subjects following UVA- and UVB-induced pigmentation, and determined that these studies did not present significant safety concerns that would require re-opening this review.

Hydroxystearic Acid – reopened

This ingredient was previously reviewed in 1999 with the conclusion that hydroxystearic acid was safe as used. The Panel agreed to reopen the safety assessment of hydroxystearic acid and add the sodium and potassium salts under the existing safe conclusion. The Panel also agreed to consider whether the following 5 additional acids should also be included in this report: hydroxycapric acid; hydroxycaprylic acid; 10-hydroxydecanoic acid; hydroxylauric acid; and 10-hydroxystearic acid.

The reported frequency of use of hydroxystearic acid has increased from 2 uses in 1996 to 99 uses in 2015, with all but one use reported in leave-on formulations. A concentration of use survey completed by the Council in 2014 indicated that the maximum concentration of use has increased from 5-10% in a deodorant formulation, as reported in the 1999 report, to 13.2% in "other" make-up preparations and 13.1% in eyeliner formulations.

Isostearamidopropyl Morpholine Lactate

The Panel reaffirmed the conclusion that isostearamidopropyl morpholine lactate is safe for use as a cosmetic ingredient in rinse-off formulations in the present practices of use and concentration.

The Panel also reaffirmed that the data were insufficient to support the safety of use in leave-on formulations. The data needed to support the safety of use in leave-on products are:

- Skin penetration; if there is significant skin penetration, then both a 28-day dermal toxicity study and reproductive and developmental toxicity study are needed;
- A genotoxicity study in a mammalian system; if positive, a 2-year dermal carcinogenicity study using National Toxicology Program methods may be needed; and
- Inhalation toxicity data.

According to information obtained from the FDA VCRP, there is one leave-on use reported for isostearamidopropyl morpholine lactate in a face and neck preparation. Pursuant to the CIR Procedures, if after 2 years these data requests are not fulfilled and this ingredient continues to have reported use in leave-on formulation according to the VCRP, the conclusion will be reclassified from insufficient to "Use Not Supported by the Data and Information Submitted to the CIR." However, if within the next 2 years the number of leave-on uses is determined to be zero, then the conclusion will be reclassified to "No Reported Use." Additionally, if data are submitted that address the above needs, the safety of the use of this ingredient in leave-on formulations will be re-evaluated.

Nonoxynols

The Panel reopened the CIR final safety assessments (published 1983 and 1999) on nonoxynols to allow for the review of new information on the following previously reviewed nonoxynols:

nonoxynol-1
nonoxynol-2
nonoxynol-3
nonoxynol-4
nonoxynol-5
nonoxynol-6
nonoxynol-7
nonoxynol-8
nonoxynol-9
nonoxynol-10
nonoxynol-12
nonoxynol-14
nonoxynol-15
nonoxynol-30
nonoxynol-40
nonoxynol-50

The Panel will determine whether to add the following ingredients after the new information has been considered. They noted that the new data on nonoxynols, summarized in the re-review document presented at the meeting, are not indicative of any new safety concerns.

nonoxynol-11
nonoxynol-13
nonoxynol-18
nonoxynol-20
nonoxynol-23
nonoxynol-25
nonoxynol-35
nonoxynol-44
nonoxynol-70
nonoxynol-100
nonoxynol-120

In the 1983 final report, the Panel concluded that nonoxynols-2, -4, -8, -9, -10, -12, -14, -15, -30, -40, and -50 are safe as cosmetic ingredients in the present practices of use and concentration. The Panel reevaluated the safety of nonoxynols-2,-4, and -8 and evaluated the safety of additional nonoxynols-1,-3, -5, -6, and -7 and concluded in a final report (published in 1999) that nonoxynols-1, -2, -3, -4, -5, -6, -7, and -8 are safe as used in rinse-off products and safe at concentrations ≤ 5% in leave-on products. This conclusion modified the previous conclusion for nonoxynols-2, -4, and -8, which had been considered safe as used in both rinse-off and leave-on products.

The Panel voted in favor of reopening the document with the intent of allowing time to gain an understanding of the basis for the European Union's (EU) ≤ 0.1% limitation on the use of nonylphenol ethoxylates (another name for nonoxynols) and nonylphenol in all products, including cosmetics. Because the EU limitation of ≤ 0.1% is less than the Panel's 5% concentration limit on nonoxynols-1, -2, -3, -4, -5, -6, -7, -8 in leave-on cosmetic products, the basis for the EU limitation, including specific toxicity concerns may warrant a change in the 5% concentration limit determined by the Panel.

The Council mentioned the likely diminished use and eventual elimination of nonoxynols in cosmetics, in light of the EU restriction on nonylphenol ethoxylates in cosmetics.

134th Meeting Notes

Director's Report

Dr. Gill mentioned the increase in the number of inquiries that CIR is receiving about the CIR process. For example, CIR received requests from international and U.S.-based organizations about concentration limits for ingredients used in cosmetic products, and questions about whether a certificate of quality can be obtained from CIR, how to get a specific ingredient reviewed and how to participate in the CIR process. The latter question, in particular, represents a category of requests that has relevance because evaluating submitted safety information is integral to fulfilling CIR's mission. Dr. Gill encouraged the submission of data from all interested parties, stating that the strength of the review process depends of the data provided to CIR. She also reemphasized the importance of the information and concerns conveyed to CIR by consumers and organizations that represent consumers, such as the Consumer Federation of America and Women's Voices for the Earth. These groups also contribute very important perspectives to the deliberations of the Panel.

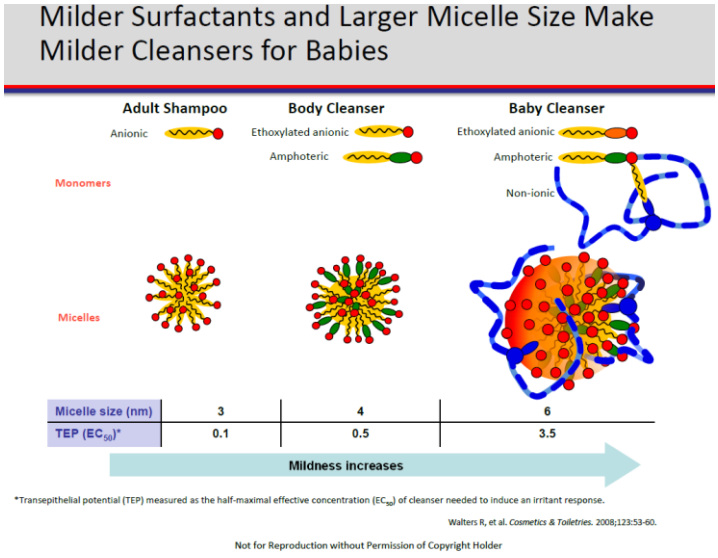
Dr. Gill also mentioned that CIR is seeking applications for the position of scientific writer. Announcements for the position are forthcoming.

Dr. Gill reminded participants that the June 15-16 meeting and all meetings held through December, 2015, will be at the The Hilton – DoubleTree Hotel, Washington, DC.

Briefing on the Dermal Diffusion Barrier and Development of Skin-Care Formulations for the Neonates and Infants

Lorena Weber Telofski, CMPP, Professionals Communications Group of Johnson & Johnson Consumer Companies, Inc., delivered a presentation to the Panel comparing the skin of neonates and infants with that of adults and discussing the use of cleansers and emollients in formulations developed specifically for the care of healthy, full-term neonates and infants.

Ms. Telofski noted that the barrier function of the skin resides primarily in the stratum corneum (SC), which protects the individual from toxicants, pathogenic microorganisms, and water loss. The barrier function is influenced by the pH of the skin, which is normally slightly acidic in older children and adults. Healthy, full-term neonates are born with a competent dermal barrier function and all of the components and layers found in adult skin, although the skin continues to develop for at least a year after birth.



Compared with mature skin, the SC of infants is thinner and is composed of smaller corneocytes, which reflects the rapid turnover of the skin cells of the infants. Cellular proliferation gradually decreases to rates characteristic of adults within 12 to 24 months of age. The SC of neonates is substantially drier than the skin of adults, although SC hydration increases precipitously, especially during the first month of life. SC hydration in infants older than about 3 months of age exceeds that of adults, indicating that there is no need for measures to prevent dehydration in healthy, full-term neonates. However, the rates of dermal water absorption and desorption and transepidermal water loss (TEWL) are greater in infants than in adults.

Ms. Telofski noted that the skin surface is alkaline at birth and acidifies quickly to exhibit pHs typical of adults within a few weeks after birth. Tear duct formation is complete soon after birth and tearing increases during the first month of life. The tear film lipid layer is thicker in infants than in adults, which reduces evaporation from the surface of the eyes.

Ms. Telofski emphasized that maintaining good hygiene and skin-barrier integrity depends on keeping the skin clean. She stated that using water alone to cleanse the skin cannot effectively remove exogenous oil and other water-insoluble and unwanted materials (e.g., saliva, nasal secretions, urine, feces and fecal enzymes) from the skin surface. She indicated that cleansers specially formulated for infants should be neutral to mildly acidic (pH 7 to 5.5) to minimize effects on skin surface pH and the potential for eye sting. The mildness of such products depends on using surfactants that yield substantially larger micelles (illustrated in the slide above, used with permission) and lower concentrations of free monomers in formulation than is typical of analogous products for adults. Further, Ms. Telofski noted that appropriate emollients (e.g., some cationic, oil-in-water emollients) in the formulation can reduce TEWL from the skin of healthy neonates without interfering with the maturation of the skin barrier. She emphasized safety assessments of products developed for neonates or infants should consider evidence of the safety of the total product formulation, as well as the individual ingredients of the formulation, for neonates and infants.

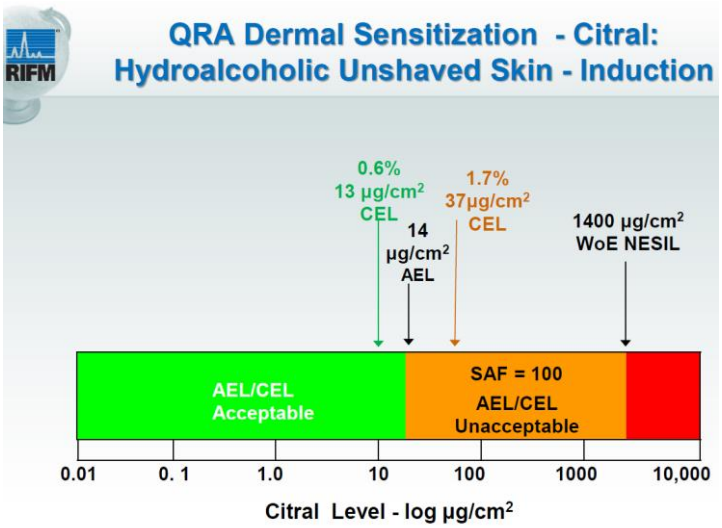
Briefing on Dermal Sensitization Quantitative Risk Assessment (QRA)

Anne Marie Api, Ph.D., Vice President of Human Health Sciences at the Research Institute for Fragrance Materials (RIFM), is a key author and principal developer of the RIFM QRA approach to evaluating the risks of inducing dermal sensitization associated with consumer exposures to fragrance ingredients. The QRA methodology is applicable to ingredients used in cosmetic formulations for purposes other than as fragrances, as well as to fragrance uses. The CIR Expert Panel has recently incorporated QRAs into some safety assessments of cosmetic ingredients.

Dr. Api noted that the goal of RIFM testing and International Fragrance Association (IFRA) standards is to prevent the induction of contact sensitization (i.e., "primary prevention") in the general population from exposures to fragrance ingredients. The QRA approach is based on a scientifically rigorous

strategy. She explained how an acceptable exposure level (AEL) is calculated for an ingredient by applying the sensitization assessment factors (SAFs) to the no expected sensitization induction level (NESIL). The approach is similar to the calculation of a US EPA reference dose (RfD) for a substance based on a no-observed-adverse-effect level (NOAEL), which represents the threshold daily exposure below which adverse effects are not likely, and uncertainty factors (UFs).

The potential for an ingredient to induce sensitization is identified based the results of pre-clinical (e.g., local lymph node assays, LLNAs), clinical (e.g., human repeat insult patch tests), and/or structure-based prediction studies.



If the data indicate the potential inducing sensitization, a NESIL is estimated using a weight-of-evidence (WoE) approach. The AEL is calculated by dividing the WoE NESIL by an overall SAF, which is the product of the SAFs selected to account for inter-individual variability, vehicle or product matrix effects, and use considerations. For example, the SAF selected to account for use considerations will depend upon how well the skin exposed to the ingredient in the tests for sensitization represent the likely dermal exposure in consumer use scenarios.

Dr. Api outlined RIFM guidelines for defining the WoE NESIL, which include use of all of the available scientifically robust data from animal and human studies and a hierarchy of such data (e.g., a NOEL from a well-run HRIPT has precedence over all other NOAELs). Conducting a confirmatory HRIPT will be considered if only LLNA are available.

The consumer exposure level (CEL) is then calculated, based on the pertinent consumer use scenarios for a product type (e.g., shampoos, underarm deodorants). The CEL is considered to be acceptable when CEL ≤ AEL.

Dr. Api used the figure above to illustrate the estimation of acceptable concentrations of citral as an ingredient in underarm deodorants. She also outlined the principal benefits and refinements considered for the further development of the approach (e.g., the incorporation of aggregate dermal exposure estimates, replacement of LLNA with non-animal test alternatives), and noted the International Dialogue for the Evaluation of Allergens (IDEA) project, which is designed to advance the framework for assessing fragrance sensitizers.

Reports Tabled

Polymerized Tetramethylcyclotetrasiloxanes

The Panel tabled the draft report on 3 polymerized tetramethylcyclotetrasiloxanes, polysilicone-2, polysilicone-4, and polysilicone-5, to allow sufficient time for industry to provide additional data. The industry requested the 6 month hold in order to provide the following data on polysilicone-2:

Physical and chemical properties
Impurities and residual monomers
Method of manufacture
Dermal sensitization and irritation

The Panel requested that industry provide the same data (identified above) for polysilicone-4 and polysilicone-5. Additionally, the following data are requested for all three ingredients:

Physical and chemical properties, especially molecular weight ranges
Concentration of use
Absorption/metabolism
If dermally absorbed: reproductive toxicity, 28-day dermal toxicity, and genotoxicity

These ingredients are each synthesized from tetramethylcyclotetrasiloxane and have a core repeating chain of -O-Si-(CH_3). Polymerized tetramethylcyclotetrasiloxanes are reported to function as antifoaming agents, hair conditioning agents, and viscosity increasing agents – nonaqueous in cosmetics.

Scientific Literature Reviews

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

alkonium clays
Pyrus malus (Apple)-Derived Ingredients
silk proteins
soy proteins

trialkyl trimellitates

Draft reports for these ingredient families, along with any unpublished data submitted by interested parties, may be presented to the Panel at its meeting on June 15-16, 2015.

- **These literature reviews are currently under development**

alkyl taurate amides and taurate salts
gingko biloba-derived ingredients
hexamethylene diisocyanate (HDI) polymers
inorganic hydroxides
keratin proteins
phosphoric acid, its simple salts, & the metaphosphates
polyglyceryl fatty acid esters
simple carbonate salts
trimellitic anhydride copolymers

- **Re-reviews scheduled for the next Panel meeting**

No new re-reviews are currently scheduled for the June meeting.

Ingredient Strategies

The Panel concurred with the CIR proposed strategies for preparing SLRs for the following 4 ingredient groups:

Brown algae derived ingredients – 65
Butyrospermum parkii (Shea) derived ingredients – 9
Helianthus annuus (Sunflower) derived ingredients – 14
Rosa canina derived ingredients – 12

Draft 2016 Ingredient Review Priorities

Interested parties are invited to comment on the inclusion of the ingredients listed below as 2016 CIR priorities. Selection of these ingredients is based on those unreviewed ingredients with the largest number of 2015 VCRP uses. Comment also is sought on the additional ingredients that might be included in each ingredient family. Proposed ingredient families may be found, starting at page 22, at the following url http://www.cir-safety.org/sites/default/files/admin_2.pdf. It is likely that not all of those listed will be chosen for work in 2016. CIR plans to finalize the proposed 2016 priority list at the June meeting.

Ingredient	**Number of formulations containing ingredient**
ethylhexyl methoxycinnamate	4783
butyl methoxydibenzoylmethane	3046
benzyl salicylate	2509
propanediol	548
linoleic acid	532
calcium stearate	370
hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer	446
ammonium acryloyldimethyltaurate/ vp copolymer	421
hydrofluorocarbon 152a	426
triethoxycaprylylsilane	409
tetrahexyldecyl ascorbate	382
panthenyl ethyl ether	378
etidronic acid	370
dicaprylyl carbonate	366
trimethyl pentanyl diisobutyrate	351
tetradecene	60
to be determined hair dye	

Next CIR Expert Panel Meeting

Monday and Tuesday, June 15-16, 2015, at The Hilton – DoubleTree Hotel, Washington, DC 20005 --- Please contact Carla Jackson (jacksonc@cir-safety.org) at CIR before the meeting if you plan to attend.