

Cosmetic Ingredient Review

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MEMORANDUM

To: CIR Expert Panel Members and Liaisons
From: Director, CIR
Subject: 125th Meeting of the CIR Expert Panel — Monday and Tuesday, December 10-11, 2012
Date: November 16, 2012

Enclosed are the agenda and accompanying materials for the 125th CIR Expert Panel Meeting to be held Monday and Tuesday, December 10-11, 2012 at the Madison Hotel, 1177 Fifteenth Street, NW, Washington, DC 20005. Phone: (202) 862-1600. Fax: (202) 785-1255. The meeting agenda includes consideration of 13 ingredient groups advancing in the process, 2 re-reviews, consideration of new data on phthalates and PEGs cocamine, and review of available data on infant skin, including dermal penetration.

One of the reports advancing and the 2 re-reviews address hair dye ingredients. A concern has been raised in Europe regarding the use of the self-test for hair dye ingredients. The Personal Care Products Council Hair Coloring Technical Committee will make a presentation.

Back in March, during the discussion of reopening the parabens report, the Panel reiterated that infants represent a susceptible subpopulation for risk assessment and that there is a need to address the potentially greater systemic absorption of ingredients through the skin in infants compared to adults when conducting cosmetic ingredient safety assessments. The Panel also expressed the view that more information may be available to inform this discussion. Dr. Boyer has gathered relevant studies regarding (1) the maturation of the stratum corneum as a barrier to absorption of xenobiotics in the perinatal, neonatal, infant and childhood periods, and (2) the maturation/transitioning that takes place in the ability of the skin to metabolize xenobiotics that penetrate the stratum corneum during those periods, and will make a brief presentation.

Schedule and hotel accommodations

We will reserve rooms for the nights of Sunday, December 9 and Monday, December 10 at the Madison. If you encounter any travel problems, please contact me on my cell phone at 301-512-7846.

Team meetings

New data - new data have been provided for one safety assessment and new data have appeared in the published literature for a second ingredient. The Panel should determine if these reports (both under buff cover) should be reopened.

1. PEGs cocamine – The Council's CIR Science and Support Committee has provided additional data regarding the safety of PEGs cocamine ingredients. Currently, the conclusion for PEG-2, -3, -5, -10, -15, and -20 cocamine is "insufficient data" (IJT 18(S1):43-50, 1999). Only PEG-5 and -15 Cocamine are in current use. If this information supports reopening this report, then the Panel should also consider adding PEG-4, -8, and -12 cocamine and other PEG fatty acid amines to the group.
2. Phthalates - Two epidemiology studies that appeared earlier in 2012 reported on associations between phthalate metabolite levels (one as measured serum levels and the other measured urinary levels) and diabetes incidence. Very recently, an epidemiology study reported on the association of urinary phthalate levels and airway inflammation. The Panel should review these data and determine if the information warrants reopening the safety assessment of phthalates. The original safety assessment of dibutyl, diethyl, and dimethyl phthalate was done in 1985 with a "safe for topical application in present practices of use and concentration" conclusion. An extensive re-review was done in 2005 and the Panel determined to not reopen the report.

Re-reviews – there are 2 safety assessments to re-review and make a determination on the need to reopen to revise the conclusion. Both reports are under buff cover. In neither case does there appear to be an opportunity to reopen to expand the scope.

1. 2-Amino-6-chloro-4-nitrophenol – this ingredient and its hydrochloride salt were reviewed previously (published in 1997) with the conclusion that these hair colorants are safe for use in hair dye formulations at concentrations up to 2.0%. The Panel had used available ocular irritation, dermal irritation, and sensitization data to determine the 2% limit. The recent use concentration data have a maximum concentration of use for 2-amino-6-chloro-4-nitrophenol of 1.5% in hair dyes and colors, suggesting that the 1997 conclusion could be reinterpreted as "safe in the present practices of use and concentration."

2. m-Phenylenediamine and m-phenylenediamine sulfate were reviewed previously (published in 1997) with the conclusion that these hair colorants are safe for use in hair dyes at concentrations up to 10%. The recent use concentration data have m-phenylenediamine at maximum concentrations ranging from 0.01% to 0.2% and, m-phenylenediamine sulfate at a maximum concentration of 1% in hair dyes and colors, suggesting that the 1997 conclusion could be reinterpreted as “safe in the present practices of use and concentration.”

Draft reports - there are 5 draft reports under green cover.

1. 6-Hydroxyindole – A scientific literature review on this hair dye ingredient was announced in August 2012. The Council has provided comments and an extensive data submission, including data that had been provided to Europe’s Scientific Committee on Consumer Products for their opinion on 6-hydroxyindole. These data have been incorporated into the report. If we have all the data we need, we can issue a tentative report. If not, we should ask for whatever additional data are needed in a formal insufficient data announcement.
2. Hydrolyzed source proteins – In May 2012, CIR issued the Scientific Literature Review (SLR) for hydrolyzed proteins. The Council has provided comments on the report, along with method of manufacturing, impurities, molecular weight, concentration of use, irritation and sensitization, genotoxicity, and phototoxicity data. These data have been incorporated into the report. If we have all the data we need, we can issue a tentative report. If not, we should ask for whatever additional data are needed in a formal insufficient data announcement.
3. Modified terephthalate polymers - CIR announced an SLR in June, 2012. Comments and unpublished data have been received from industry and incorporated into the report. We have relied on the extensive evaluation of these polymers as used in medical implants done by FDA’s Center for Devices and Radiological Health. FDA has approved the use of terephthalate polymers in surgical sutures, esophageal dilators, and surgical mesh. One safety issue has arisen that appears to be specific to cosmetic usage. Glitter is created by the chopping up sheets of the polymers in a manner that leaves jagged edges (to promote adhesion). If these become imbedded in the eye, such glitter may be difficult to remove. If we have all the data we need, we can issue a tentative report. If not, we should ask for whatever additional data are needed in a formal insufficient data announcement.
4. Source amino acids - In May 2012, CIR issued an SLR for source amino acids. These ingredients each are mixtures of amino acids derived from specific plant and animal sources. Accordingly, the group is given the name: source amino acids – indicating that they come from specific sources. We’ve relied heavily on the GRAS direct food additive status of the common amino acids since these ingredients are, after all, amino acids, just from specific sources. In the SLR, we flagged that we would need data on method of manufacturing, impurities and approximate composition for cosmetic grade ingredients, physical properties, and dermal irritation and sensitization data. We’ve received some of these data, but not all. If we have all the data we need, we can issue a tentative report. If not, we should ask for whatever additional data are needed in a formal insufficient data announcement.
5. Talc - The SLR for talc was issued on August 21, 2012. One old issue regarding talc and asbestos we think is a non-issue because specifications for cosmetic talc state that it must be asbestos-free and that it does not contain asbestiform fibers. This safety assessment has generated a good deal of interest, and a number of comments and data have been received. Where the “data” were from scientific studies we have captured that information, published and unpublished. Where the “data” were press reports, we did not capture that information. If we have all the data we need, we can issue a tentative report. If not, we should ask for whatever additional data are needed in a formal insufficient data announcement.

Tentative reports – there are 6 tentative reports under pink cover.

1. Achillea millefolium-derived ingredients - In June, 2012, the Panel reopened this “insufficient data” report. The Council’s CIR Science and Support Committee had submitted published and unpublished data relating to each of the 5 data needs identified by the Panel back in 2001. The Panel determined that the new data likely addressed the data needs and suggested that these ingredients may be safe for use in cosmetics, so a draft tentative amended report has been prepared. The draft tentative amended report now includes all of the achillea millefolium-derived ingredients. The Panel should review the tentative amended report and confirm that it is appropriate to add the 4 new ingredients. Then the Panel should confirm that the new data satisfy the needs of the Panel. The Panel should review the draft tentative conclusion, and develop a discussion section which presents the rationale for the conclusion.
2. Alkyl esters - This report was re-opened back in March, not to add new data, but to expand the safety assessment to include similar ingredients. This report was tabled at the September meeting so that historical use data from reports on ingredients previously reviewed by CIR could be added to the safety assessment. You will find these data incorporated into Table 8. The Panel deleted 16 alkyl ethylhexanoates from the report so that they could be handled separately. The Council has provided some additional data on the remaining 238 alkyl esters. The Panel should review the additional data, the draft tentative conclusion, and the draft discussion section which presents the rationale for the conclusion.

3. Alkyl ethylhexanoates - Alkyl ethylhexanoates were originally included in a re-review of the alkyl esters family of ingredients (see above). Because of concern over the possible reproductive risk associated with 2-ethylhexanoic acid, a possible metabolite of the alkyl ethylhexanoates that makes these ingredients distinct from other alkyl esters, the Expert Panel determined that it was not appropriate to include the ethylhexanoates in the safety assessment on the alkyl esters. However, the Panel determined to proceed to consider an amended safety assessment of the 16 alkyl ethylhexanoates based on a re-review and expansion of the cetearyl ethylhexanoate report from 1982, which was reaffirmed in 2006 as safe as used, but oddly, not expanded. At this meeting, if the Panel is still in agreement that the data in the original safety assessment on cetearyl ethylhexanoate can be extrapolated to determine the safety of the additional 15 alkyl ethylhexanoates, a tentative conclusion should then be issued. The Panel has also reviewed a number of the constituent alcohols; these data may also be useful in determining safety. The Panel should review the additional data, the draft tentative conclusion, and the draft discussion section which presents the rationale for the conclusion.
4. *Hypericum perforatum*-derived ingredients - At the June, 2012 meeting, the CIR Expert Panel reopened this “insufficient data” report. A large amount of new data were provided by the CIR Science and Support Committee. The Panel determined that the new data likely addressed the data needs and suggested that these ingredients may be safe for use in cosmetics, so a draft tentative amended report has been prepared. In addition, the relevant data from the European Medicines Agency’s review of *Hypericum perforatum* (2009) have been added to the report along with other published studies. The Panel should review the tentative amended report and confirm that it is appropriate to add the new ingredients. Then the Panel should confirm that the new data satisfy the needs of the Panel. The Panel should review the draft tentative conclusion, and the develop a discussion section which presents the rationale for the conclusion.
5. Methyl glucose polyethers and esters - An Insufficient Data Announcement with the following data requests was issued at the September 2012 Panel meeting: (1) skin penetration data on the polyethers; if dermal absorption occurs, then reproductive and developmental toxicity data may be needed; (2) genotoxicity data on the polyethers and esters; (3) repeated insult patch test (RIPT) data on methyl glucose dioleate to confirm safety at the maximum use concentration of 2%; and (4) study details for the RIPT on methyl glucose sesquistearate included in the safety assessment. We’ve received a lot of data which have been incorporated. If these data are sufficient, the Panel should issue a tentative report for public comment with the appropriate tentative conclusion and develop a discussion section which presents the rationale for the tentative conclusion. If the data remain insufficient, then a tentative report with an insufficient data conclusion should be issued for public comment.
6. Nylon ingredients - An Insufficient Data Announcement with the following data requests was issued at the June 2012 Panel meeting: (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 monomer, dodecanolactam. We have received some of these data, but not all. Those data that were received have been incorporated in this draft. If these data are sufficient, the Panel should issue a tentative report for public comment with the appropriate tentative conclusion and develop a discussion section which presents the rationale for the tentative conclusion. If the data remain insufficient, then a tentative report with an insufficient data conclusion should be issued for public comment.

Final reports - there are 2 final reports under blue cover. After reviewing these drafts, especially the rationale in the discussion section, the Panel should issue them as final reports.

1. PEGylated oils – At the September 2012 meeting, the Panel issued a tentative amended safety assessment on PEGylated Oils with the conclusion that these ingredients are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating. One ingredient has an updated name, but no other data were received. The Council provided technical comments on the report, which have been considered.
2. Tin(IV) oxide - At the September 2012 meeting, the Panel issued a tentative report with a conclusion stating that tin(IV) oxide is safe in the present practices of use and concentration. Technical comments were received from the Council and have been addressed.

Full Panel Meeting

Remember, the breakfast buffet will open at 8:00 am and the meeting starts at 8:30 am on day 2.

The Panel will consider the 2 reports to be issued as final safety assessments, followed by the rest of the reports advancing in the process and finish with the infant skin consideration..

It is likely that the full Panel session will conclude before lunch on day 2, so plan your travel accordingly. Have a safe journey.

125th Cosmetic Ingredient Review Expert Panel Meeting

December 10-11, 2012

Monday, December 10

8:00 am	CONTINENTAL BREAKFAST		
8:30 am	WELCOME TO THE 125th EXPERT PANEL TEAM MEETINGS	Drs. Bergfeld/Andersen	
8:40 am	Hair Dye Self-Testing	Carsten Goebel, Procter and Gamble, on behalf of the Council's Hair Coloring Technical Committee	
9:20 am	Infant Skin	Dr. Boyer	
10:00 am	TEAM MEETINGS	Drs. Marks/Belsito	
	Dr. Marks' Team	Dr. Belsito's Team	
Blue (WJ)	Tin(IV) oxide	Buff (MF)	2-Amino-6-chloro-4-nitrophenol (re-review)
Buff (WJ)	m-Phenylenediamines (re-review)	Pink (MF)	Alkyl ethylhexanoates
Pink (WJ)	Methyl glucose polyethers & esters	Pink (MF)	Alkyl esters
Blue (CB)	PEGylated oils	Green (MF/IB)	Talc
Pink (CB)	Nylon	Buff (AA/IB)	Phthalates – new data
Green (CB)	6-Hydroxyindole	Buff (AA/LG)	PEGs cocamine – new data
Green (CB)	Source amino acids	Blue (WJ)	Tin(IV) oxide
Green (CB)	Hydrolyzed source proteins	Buff (WJ)	m-Phenylenediamines (re-review)
Pink (LB)	Achillea millefolium-derived ingredients	Pink (WJ)	Methyl glucose polyethers & esters
Pink (LB)	Hypericum perforatum-derived ingredients	Green (CB)	Source amino acids
Green (LB)	Modified terephthalate polymers	Green (CB)	Hydrolyzed source proteins
Buff (AA/IB)	Phthalates – new data	Green (CB)	6-Hydroxyindole
Buff (AA/LG)	PEGs cocamine – new data	Pink (CB)	Nylon
Pink (MF)	Alkyl esters	Blue (CB)	PEGylated oils
Pink (MF)	Alkyl ethylhexanoates	Green (LB)	Modified terephthalate polymers
Green (MF/IB)	Talc	Pink (LB)	Hypericum perforatum-derived ingredients
Buff (MF)	2-Amino-6-chloro-4-nitrophenol (re-review)	Pink (LB)	Achillea millefolium-derived ingredients
Noon	Lunch		
1:00 pm	Team meetings continue as needed		
5:15 pm	ADJOURN DAY 1 SESSION		

NOTE: The order of presentation and discussion of each topic will be maintained. However, the scheduled times may be accelerated or delayed depending upon the time required for the Expert Panel to complete its review of each subject.

Tuesday, December 11

8:00 am	CONTINENTAL BREAKFAST	
8:30 am	WELCOME TO THE 125th FULL CIR EXPERT PANEL MEETING	
8:45 am	MINUTES OF THE September, 2012 EXPERT PANEL MEETING	Dr. Bergfeld
9:00 am	DIRECTOR'S REPORT	Dr. Andersen
9:30 am	FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, RE-REVIEWS, and OTHER DISCUSSION ITEMS	

Final Reports

Blue (WJ)	Tin(IV) oxide - Dr. Marks reports
Blue (CB)	PEGylated oils - Dr. Belsito reports

Reports Advancing

Pink (CB)	Nylon - Dr. Marks reports
Green (CB)	Source amino acids - Dr. Belsito reports
Green (CB)	Hydrolyzed source proteins - Dr. Marks reports
Green (CB)	6-Hydroxyindole - Dr. Belsito reports
Pink (LB)	Hypericum perforatum-derived ingredients - Dr. Marks reports
Pink (LB)	Achillea millefolium-derived ingredients - Dr. Belsito reports
Green (LB)	Modified terephthalate polymers – Dr. Marks reports
Pink (MF)	Alkyl esters - Dr. Belsito reports
Pink (MF)	Alkyl ethylhexanoates - Dr. Marks reports
Green (MF/IB)	Talc - Dr. Belsito reports
Buff (MF)	2-Amino-6-chloro-4-nitrophenol (re-review) - Dr. Marks reports
Buff (WJ)	m-Phenylenediamine (re-review) - Dr. Belsito reports
Pink (WJ)	Methyl glucose polyethers & esters - Dr. Marks reports

New Data

Buff (AA/IB)	Phthalates – Dr. Belsito reports
Buff (AA/LG)	PEGs Cocamine - Dr. Marks reports

Other Items

Buff (IB)	Infant skin
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ADJOURN - Next meeting *Monday and Tuesday, December 10-11, 2012*

NOTE: The order of presentation and discussion of each topic will be maintained. However, the scheduled times may be accelerated or delayed depending upon the time required for the Expert Panel to complete its review of each subject.

Cosmetic Ingredient Review

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Since 1976*



ONE HUNDRED TWENTY-FOURTH MEETING

OF THE

EXPERT PANEL

September 10-11, 2012

The Madison Hotel

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chair

Donald V. Belsito, M.D.

Ronald A. Hill, Ph.D.

Curtis D. Klaassen, Ph.D.

Daniel C. Liebler, Ph.D.

James G. Marks, Jr., M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

Paul W. Snyder, D.V.M., Ph.D.

Liaison Representatives

Consumer

Rachel Weintraub, Esq.

Industry

Halyna Breslawec, Ph.D.

Government

Linda Katz, MD., M.P.H.
(ABSENT)

Adopted (Date)

Wilma F. Bergfeld, M.D.

Others Present at Meeting

F. Alan Andersen	CIR
Yutaka Aoki	Kanebo Cosmetics
Robeena Aziz	FDA
Lillian Becker	CIR
Ivan Boyer	CIR
Christina Burnett	CIR
Kapal Dewan	FDA
Carol Eisenmann	PCPC
Monice Fiume	CIR
Kevin Fries	CIR
Lillian Gill	CIR
Bart Heldreth	CIR
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
Akiho Kinoshita	Shiseido
Dennis Laba	Presperse
Linda Loretz	PCPC
Stanley R. Milstein	FDA
Lauren Nardella	The Rose Sheet
Diego Rua	FDA
Noriko Shibuya	Shiseido
Julie Skare	Procter & Gamble
David Steinberg	Steinberg & Associates
Donna Webster	Herbalife
Jeremy Wong	Estee Lauder
Sherwin Yan	Colgate-Palmolive

CHAIRMAN'S OPENING REMARKS

The 124th meeting of the CIR Expert Panel was called to order by Dr. Bergfeld at 8:30 a.m. on Tuesday, September 11, 2012. She stated that over 17 ingredients were reviewed in Teams on the preceding day and that these ingredients are included on today's agenda. Dr. Bergfeld noted that the reports scheduled for review are of a distinct quality. Tables summarizing studies are very helpful and the expanded discussion section is clearly understood. She thanked members of the CIR staff for their efforts and the Expert Panel for its participation in the review process.

APPROVAL OF MINUTES

The minutes of the June 11-12, 2012 CIR Expert Panel meeting were unanimously approved.

DIRECTOR'S REPORT

- ◆Dr. Andersen noted that the Chairman of the Personal Care Products Council Board of Directors, Scott Beattie, had expressed an interest in attending today's Panel meeting, but was unable to attend due to a scheduling conflict.
- ◆The portion of CIR's website that is used for posting Panel meeting materials is working as designed and implemented. However, functionality issues relating to use of this website are evident, and a significant effort to ensure that users are able to find CIR safety assessments at the website needs to be made. In response to questions relating to ingredient information accessible to dermatologists at the website and associated costs, Dr. Andersen said that the proposed plan would allow user access to the Expert Panel's conclusions as well as the full safety assessments free of charge. However, the CIR Compendium will be sold to the general public. The most recent version of the Compendium, current through June of this year, is nearing completion and document pdf's will be made available to Panel members.
- ◆ Re-review documents on 2-amino-6-chloro-4-nitrophenol and m-phenylenediamine hair dye ingredients are scheduled for review at the December 10-11, 2012 Expert Panel meeting. This means that concerns, raised in Europe, regarding risks potentially associated with the testing of hair dyes on a small area of skin prior to use will need to be addressed. Whether or not this type of testing is a good practice needs to be investigated.
- ◆Several new studies on phthalates are available, some of which relate to diabetes risk in the elderly. Thus, the impact of these data on the CIR safety assessment of phthalates needs to be investigated. This discussion will also be included as an agenda item for the December Panel meeting.
- ◆CIR may receive information from the Professional Keratin Smoothing Council (PKSC) on the impact of its programs to improve the conditions under which hair smoothing products containing formaldehyde and/or methylene glycol are used. A presentation by the PKSC may take place at the December meeting or a subsequent Panel meeting.
- ◆Approximately 600 ingredients may be reviewed by CIR in 2013.

Final Safety Assessments

***α*-Amino Acids**

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

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

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

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

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

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

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

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

Borosilicate Glasses

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

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

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

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

Chlorphenesin

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

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

Dialkyl Malates

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

dibutyloctyl malate*	diisoamyl malate*
di-C12-13 alkyl malate	diisostearyl malate
diethylhexyl malate	dioctyl dodecyl malate*

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

These ingredients have general functionality in cosmetics as skin conditioning agents and are used at concentrations up to 82%. While complete toxicological data were not available for each of the ingredients, the data that were available indicated that dialkyl malates were not systemic toxicants and were not genotoxic, irritating, nor sensitizing in mammalian and/or human studies. These data could be extrapolated to support the safety of the entire group.

Dimethicone Crosspolymers

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

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

vinyl dimethyl/trimethylsiloxysilicate/dimethicone crosspolymer*

vinyl dimethyl/trimethylsiloxysilicate stearyl dimethicone crosspolymer*

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

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

Microbial Polysaccharide Gums

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

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

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

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

Panax spp. Root-Derived Ingredients

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

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

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

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

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

Polyether Lanolins

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

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

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

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

Vitis Vinifera (Grape)-Derived Ingredients

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

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

vitis vinifera (grape) vine extract;
vitis vinifera (grape) vine sap;*

hydrolyzed grape fruit;*
hydrolyzed grape skin.*

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

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

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

Tentative Safety Assessments

PEGylated Oils

The CIR Expert Panel issued a tentative amended safety assessment for public comment with the conclusion that PEGylated Oils are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating. This conclusion supersedes the earlier conclusion issued by the Expert Panel in 1997 for PEGs castor oils.

The 130 ingredients included in this safety assessment are:

PEG-2 castor oil*	PEG-5 hydrogenated castor oil*
PEG-3 castor oil*	PEG-6 hydrogenated castor oil*
PEG-4 castor oil*	PEG-7 hydrogenated castor oil
PEG-5 castor oil*	PEG-8 hydrogenated castor oil*
PEG-8 castor oil*	hydrogenated castor oil PEG-8 esters*
PEG-9 castor oil	PEG-10 hydrogenated castor oil
PEG-10 castor oil*	PEG-16 hydrogenated castor oil
PEG-11 castor oil*	PEG-20 hydrogenated castor oil
PEG-15 castor oil*	PEG-25 hydrogenated castor oil
PEG-16 castor oil*	PEG-30 hydrogenated castor oil
PEG-20 castor oil*	PEG-35 hydrogenated castor oil
PEG-25 castor oil	PEG-40 hydrogenated castor oil
PEG-26 castor oil*	PEG-45 hydrogenated castor oil
PEG-29 castor oil*	PEG-50 hydrogenated castor oil
PEG-30 castor oil	PEG-54 hydrogenated castor oil*
PEG-33 castor oil	PEG-55 hydrogenated castor oil*
PEG-35 castor oil	PEG-60 hydrogenated castor oil
PEG-36 castor oil	PEG-65 hydrogenated castor oil*
PEG-40 castor oil	PEG-80 hydrogenated castor oil
PEG-44 castor oil*	PEG-100 hydrogenated castor oil
PEG-50 castor oil	PEG-200 hydrogenated castor oil*
PEG-54 castor oil*	PEG-5 hydrogenated castor oil isostearate*
PEG-55 castor oil*	PEG-10 hydrogenated castor oil isostearate*
PEG-60 castor oil	PEG-15 hydrogenated castor oil isostearate*
PEG-75 castor oil*	PEG-20 hydrogenated castor oil isostearate*
PEG-80 castor oil*	PEG-30 hydrogenated castor oil isostearate*
PEG-100 castor oil*	PEG-40 hydrogenated castor oil isostearate*
PEG-200 castor oil*	PEG-50 hydrogenated castor oil isostearate*
PEG-18 castor oil dioleate*	PEG-58 hydrogenated castor oil isostearate*
PEG-60 castor oil isostearate*	PEG-20 hydrogenated castor oil laurate*
PEG-2 hydrogenated castor oil	PEG-30 hydrogenated castor oil laurate*

PEG-40 hydrogenated castor oil laurate*	hydrogenated palm/palm kernel oil PEG-6 esters
PEG-50 hydrogenated castor oil laurate*	jojoba oil PEG-8 esters
PEG-60 hydrogenated castor oil laurate*	jojoba oil PEG-150 esters*
PEG-20 hydrogenated castor oil pca isostearate*	linseed oil PEG-8 esters*
PEG-30 hydrogenated castor oil pca isostearate*	macadamia ternifolia seed oil PEG-8 esters*
PEG-40 hydrogenated castor oil pca isostearate	mango seed oil PEG-70 esters*
PEG-60 hydrogenated castor oil pca isostearate*	mink oil PEG-13 esters*
PEG-50 hydrogenated castor oil succinate	olive oil PEG-6 esters*
potassium PEG-50 hydrogenated castor oil succinate*	olive oil PEG-7 esters
sodium PEG-50 hydrogenated castor oil succinate*	olive oil PEG-8 esters*
PEG-5 hydrogenated castor oil triisostearate*	olive oil PEG-10 esters
PEG-10 hydrogenated castor oil triisostearate*	orbignya oleifera seed oil PEG-8 esters*
PEG-15 hydrogenated castor oil triisostearate*	palm oil PEG-8 esters*
PEG-20 hydrogenated castor oil triisostearate	passiflora edulis seed oils PEG-8 esters*
PEG-30 hydrogenated castor oil triisostearate*	peanut oil PEG-6 esters*
PEG-40 hydrogenated castor oil triisostearate	PEG-75 crambe abyssinica seed oil*
PEG-50 hydrogenated castor oil triisostearate*	PEG-75 meadowfoam oil
PEG-60 hydrogenated castor oil triisostearate*	pumpkin seed oil PEG-8 esters*
adansonia digitata seed oil PEG-8 esters*	rapeseed oil PEG-3 esters*
almond oil PEG-6 esters*	rapeseed oil PEG-20 esters*
almond oil PEG-8 esters *	raspberry seed oil PEG-8 esters*
apricot kernel oil PEG-6 esters	safflower seed oil PEG-8 esters*
apricot kernel oil PEG-8 esters*	schinziophyton rautanenii kernel oil PEG-8 esters*
apricot kernel oil PEG-40 esters*	sclerocarya birrea seed oil PEG-8 esters*
argan oil PEG-8 esters*	sesame seed oil PEG-8 esters*
avocado oil PEG-8 esters*	soybean oil PEG-8 esters*
avocado oil PEG-11 esters	soybean oil PEG-20 esters*
bertholletia excelsa seed oil PEG-8 esters*	soybean oil PEG-36 esters*
borage seed oil PEG-8 esters*	sunflower seed oil PEG-8 esters*
coconut oil PEG-10 esters	sunflower seed oil PEG-32 esters*
corn oil PEG-6 esters*	sweet almond oil PEG-8 esters*
corn oil PEG-8 esters*	watermelon seed oil PEG-8 esters*
grape seed oil PEG-8 esters	wheat germ oil PEG-40 butyloctanol esters*
hazel seed oil PEG-8 esters*	wheat germ oil PEG-8 esters*

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

PEGylated Oils is the name CIR devised to describe this large group of cosmetic ingredients. These ingredients are mixtures of the etherification and transesterification products of fatty acid glycerides and fatty acids from plant sources and equivalents of ethylene oxide to produce the desired PEG length. Because of the nature of the process by which these ingredients are produced, PEG compounds unattached to glycerides or fatty acid groups will be present. Overall, PEGylated oils are complex mixtures of structurally related molecules. The Panel determined that the available data in previous safety assessments of PEGs and of plant-derived fatty acids strongly supported the safety of PEGylated oils. In addition, the Panel considered that the available data on PEGs castor oils and PEGs hydrogenated castor oils could be “read across” to support the safety of the entire group.

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

The Expert Panel noted that the earlier safety assessment of PEG castor oils specified safe up to a 50% use concentration. As PEGs castor oils and the rest of the PEGylated oils now are used at concentrations below 50% in leave-on products, the Panel determined that a concentration limit need no longer be specified. Products using these ingredients should be formulated to be non-irritating.

Tin(IV) Oxide

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

This ingredient is a widely used cosmetic abrasive, bulking, and opacifying agent. Throughout the report, the valence of tin oxide used in studies will be specified and, if not available, the absence of this information will be noted. The Panel asserted that, while there are

no carcinogenicity or reproductive and developmental toxicity data, these endpoints are not of concern because this ingredient is insoluble and would not be percutaneously absorbed.

Insufficient Data Announcement

Methyl Glucose Polyethers and Esters

The CIR Expert Panel requested additional data to support the safety of methyl glucose polyethers and esters.

The additional data needed are: (1) skin penetration data on the polyethers; if dermal absorption occurs, then reproductive and developmental toxicity data may be needed; (2) genotoxicity data on the polyethers and esters; (3) repeated insult patch test (RIPT) data on methyl glucose dioleate to confirm safety at the maximum use concentration of 2%; and (4) study details for the RIPT on methyl glucose sesquistearate included in the safety assessment.

The 25 methyl glucose polyethers and esters in this safety assessment are:

Esters

methyl glucose caprylate/caprate
methyl glucose dioleate
methyl glucose isostearate
methyl glucose laurate
methyl glucose sesquicaprylate/
sesquicaprate
methyl glucose sesquicoate
methyl glucose sesquiosostearate
methyl glucose sesquilaurate
methyl glucose sesquioleate
methyl glucose sesquistearate

Polyethers

PPG-10 methyl glucose ether
PPG-20 methyl glucose ether
PPG-25 methyl glucose ether
methyl gluceth-10
methyl gluceth-20

Esters and polyethers

PEG-120 methyl glucose dioleate
PEG-20 methyl glucose distearate
PEG-80 methyl glucose laurate
PEG-20 methyl glucose
sesquicaprylate/ sesquicaprate
PEG-20 methyl glucose sesquilaurate
PEG-20 methyl glucose sesquistearate
PEG-120 methyl glucose triisostearate
PEG-120 methyl glucose trioleate
PPG-20 methyl glucose ether acetate
PPG-20 methyl glucose ether
distearate

Methyl glucose polyethers are widely used skin and hair conditioning agents. Methyl glucose esters are used only as skin conditioning agents in cosmetic products.

Because either methyl glucose or methyl glucoside is the backbone of these methyl glucose polyether and ester chemical structures and would likely be released by the hydrolysis of these ingredients in the skin, the Panel requested literature searches on methyl glucose and methyl glucoside to identify data that may be pertinent to this safety assessment. Industry is alerted that any available unpublished data on methyl glucose and methyl glucoside should be submitted to CIR.

Re-review

Retinol and Retinyl Palmitate – reopened

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

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

New Data

Parabens

The CIR Expert Panel determined to not reopen the safety assessment of methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben and benzylparaben. One new study suggesting that the preservative function of parabens might be linked to allergic sensitization, while other potential endocrine disrupting chemicals were not linked to this condition, was considered by the CIR Expert Panel. The Panel also reviewed a study that measured paraben concentrations as a function of location in breast tissue. In addition, an in vitro study of immortalized but untransformed human breast epithelial cells in culture reported cell transformation at concentrations that were considered to be comparable to the concentrations measured in some of the breast tissue studied. The Panel determined that these data are not relevant to the assessment of the safety of parabens in cosmetics. The Panel reaffirmed that parabens are safe in the present practices of use and concentration. The Panel suggested that their extensive discussion about these data would be important to communicate to the public and to the scientific community and that a detailed discussion should be prepared for posting on the CIR website, for a press release, and for a letter to the editor of an appropriate scientific journal.

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

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

Triclosan

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

Cherednichenko G et al. 2012. Triclosan impairs excitation-contraction coupling and Ca²⁺ dynamics in striated muscle. *Proceedings of the National Academy of Sciences* 109(35): 14158-14163.

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

Reports Tabled – alkyl esters and fatty acid amidopropyl dimethylamines

Alkyl Esters - The CIR Expert Panel tabled further discussion of the alkyl esters report.

This re-review includes more than 50 ingredients that have been reviewed previously by the CIR. During its discussion of this ingredient group, the Panel noted that the current use concentration of a number of these previously reviewed ingredients is greater than the use concentration reported at the time of the original safety assessment. While data may be available to support the current, higher use concentrations, the Panel wanted to more closely examine the existing data to ensure that the safety of use at the higher concentrations is supported. Interested parties are encouraged to submit any available unpublished data supporting the safety of such higher use concentrations.

Prior to tabling the report, the Panel removed the 16 ethylhexanoate ingredients that were included in the group because of concern for the reproductive risk of exposure to 2-ethylhexanoic acid, which is a possible metabolite of these ingredients.

The remaining 238 alkyl esters included in this group are listed below, and those that were reviewed previously are indicated by †.

arachidyl behenate	behenyl beeswax	behenyl/isostearyl beeswax
arachidyl erucate	behenyl behenate	butyl avocadate
arachidyl propionate†	behenyl erucate	butyl babassuate
batyl isostearate	behenyl isostearate	butyl isostearate
batyl stearate	behenyl olivate	butyl myristate†

butyl oleate
 butyl stearate†
 butyloctyl beeswax
 butyloctyl behenate
 butyloctyl candelillate
 butyloctyl cetearate
 butyloctyl oleate
 butyloctyl palmitate
 C10-40 isoalkyl acid octyldodecanol esters
 C14-30 alkyl beeswax
 C16-36 alkyl stearate
 C18-38 alkyl beeswax
 C18-38 alkyl c24-54 acid ester
 C20-40 alkyl behenate
 C20-40 alkyl stearate
 C30-50 alkyl beeswax
 C30-50 alkyl stearate
 C32-36 isoalkyl stearate
 C40-60 alkyl stearate
 C4-5 isoalkyl cocoate
 caprylyl butyrate
 caprylyl caprylate
 caprylyl eicosenoate
 cetearyl behenate
 cetearyl candelillate
 cetearyl isononanoate†
 cetearyl nonanoate†
 cetearyl olivate
 cetearyl palmate
 cetearyl palmitate
 cetearyl rice branate
 cetearyl stearate
 cetyl babassuate
 cetyl behenate
 cetyl caprate
 cetyl caprylate
 cetyl dimethyloctanoate
 cetyl esters
 cetyl isononanoate†
 cetyl laurate
 cetyl myristate†
 cetyl oleate
 cetyl palmitate†
 cetyl ricinoleate†
 cetyl stearate†
 cetyl tallowate
 chimyl isostearate
 chimyl stearate
 coco-caprylate
 coco-caprylate/caprato
 coco-rapeseedate
 decyl castorate
 decyl cocoate†
 decyl isostearate
 decyl jojobate
 decyl laurate
 decyl myristate†
 decyl oleate†
 decyl olivate
 decyl palmitate
 decyltetradecyl cetearate

erucyl arachidate
 erucyl erucate
 erucyl oleate
 ethylhexyl adipate/palmitate/stearate
 ethylhexyl C10-40 isoalkyl acidate
 ethylhexyl cocoate†
 ethylhexyl hydroxystearate
 ethylhexyl isononanoate†
 ethylhexyl isopalmitate
 ethylhexyl isostearate
 ethylhexyl laurate
 ethylhexyl myristate†
 ethylhexyl neopentanoate
 ethylhexyl oleate
 ethylhexyl olivate
 ethylhexyl palmitate†
 ethylhexyl pelargonate†
 ethylhexyl stearate†
 heptyl undecylenate
 heptylundecyl hydroxystearate
 hexyl isostearate
 hexyl laurate
 hexyldecyl hexyldecanoate
 hexyldecyl isostearate
 hexyldecyl laurate
 hexyldecyl oleate
 hexyldecyl palmitate
 hexyldecyl stearate
 hexyldodecyl/octyldecyl hydroxystearate
 hydrogenated castor oil behenyl esters
 hydrogenated castor oil cetyl esters
 hydrogenated castor oil stearyl esters
 hydrogenated ethylhexyl olivate
 hydrogenated ethylhexyl sesamate
 hydrogenated isocetyl olivate
 hydrogenated isopropyl jojobate
 hydroxycetyl isostearate
 hydroxyoctacosanyl hydroxystearate
 isoamyl laurate
 isobutyl myristate†
 isobutyl palmitate
 isobutyl perlargonate†
 isobutyl stearate†
 isobutyl tallowate
 isocetyl behenate
 isocetyl isodecanoate
 isocetyl isostearate
 isocetyl laurate
 isocetyl myristate
 isocetyl palmitate
 isocetyl stearate†
 isodecyl cocoate†
 isodecyl hydroxystearate
 isodecyl isononanoate†
 isodecyl laurate
 isodecyl myristate†
 isodecyl neopentanoate
 isodecyl oleate†
 isodecyl palmitate
 isodecyl stearate
 isohexyl caprate

isohexyl laurate
 isohexyl neopentanoate
 isohexyl palmitate
 isolauryl behenate
 isononyl isononanoate†
 isoocetyl caprylate/caprato
 isoocetyl tallate
 isopropyl isostearate
 isopropyl arachidate
 isopropyl avocadate
 isopropyl babassuate
 isopropyl behenate
 isopropyl hydroxystearate
 isopropyl isostearate†
 isopropyl jojobate
 isopropyl laurate
 isopropyl linoleate
 isopropyl myristate†
 isopropyl oleate
 isopropyl palmitate†
 isopropyl ricinoleate†
 isopropyl sorbate
 isopropyl stearate†
 isopropyl tallowate
 isostearyl avocadate
 isostearyl behenate
 isostearyl erucate
 isostearyl hydroxystearate
 isostearyl isononanoate†
 isostearyl isostearate
 isostearyl laurate
 isostearyl linoleate
 isostearyl myristate†
 isostearyl neopentanoate†
 isostearyl palmitate
 isotridecyl isononanoate†
 isotridecyl laurate
 isotridecyl myristate†
 isotridecyl stearate
 lauryl behenate
 lauryl cocoate†
 lauryl isostearate
 lauryl laurate
 lauryl myristate†
 lauryl oleate
 lauryl palmitate
 lauryl stearate
 lignoceryl erucate
 myristyl isostearate
 myristyl laurate
 myristyl myristate†
 myristyl neopentanoate
 myristyl stearate†
 octyldecyl oleate
 octyldodecyl avocadoate
 octyldodecyl beeswax
 octyldodecyl behenate
 octyldodecyl cocoate†
 octyldodecyl erucate
 octyldodecyl hydroxystearate
 octyldodecyl isostearate
 octyldodecyl meadowfoamate

octyldodecyl myristate†	oleyl oleate	tetradecyloctadecyl behenate
octyldodecyl neodecanoate	oleyl stearate	tetradecyloctadecyl hexyldecanoate
octyldodecyl neopentanoate	propylheptyl caprylate	tetradecyloctadecyl myristate†
octyldodecyl octyldodecanoate	stearyl beeswax	tetradecyloctadecyl stearate
octyldodecyl oleate	stearyl behenate†	tetradecylpropionates
octyldodecyl olivate	stearyl caprylate†	tridecyl behenate
octyldodecyl ricinoleate†	stearyl erucate	tridecyl cocoate†
octyldodecyl safflowerate	stearyl heptanoate†	tridecyl erucate
octyldodecyl stearate	stearyl linoleate	tridecyl isononanoate†
oleyl arachidate	stearyl olivate†	tridecyl laurate
oleyl erucate	stearyl palmitate†	tridecyl myristate†
oleyl linoleate	stearyl stearate†	tridecyl neopentanoate
oleyl myristate†	tetradecyleicosyl stearate	tridecyl stearate

Fatty Acid Amidopropyl Dimethylamines – further discussion of the fatty acid amidopropyl dimethylamines group report was tabled.

The Panel was informed that a dossier including data from additional studies on stearamidopropyl dimethylamine is being prepared under the auspices of the REACH program in Europe. The Panel anticipates that it will receive the data mid-2013 and determined that this safety assessment should include such data.

While awaiting these data, the CIR Expert Panel is alerting the public that the data in the current safety assessment are insufficient to support the safety of the fatty acid amidopropyl dimethylamine ingredients. The additional data needed include: (1) percutaneous absorption data on cocamidopropyl 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 24 fatty acid amidopropyl dimethylamines in this safety assessment are:

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

*Not reported to be in current use.

2013 Review Priorities

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

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

- ceramide 3 – 377 uses
- hydroxypropyl bis(*n*-hydroxyethyl-*p*-phenylenediamine) HCl – 75 uses

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

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

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